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CONTROLLED SEARCH FOR NEUROLOGICAL DISTURBANCES ASSOCIATED WITH ASTEROL APPLICATIONS

Preliminary Report

JEAN HOLOWACH, M.D.
JAMES L. O'LEARY, M.D.
AND
DON L. THURSTON, M.D.
ST. LOUIS

EXTENSIVE laboratory and clinical studies * have proved that 5% Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) dihydrochloride is an effective topical remedy for tinea capitis. Initial laboratory and clinical studies indicated that Asterol had a relatively low toxicity. The L. $D._{50}$ of the drug in mice is 375 mg. per kilogram of body weight subcutaneously and 500 mg. orally. Evaluation of skin irritation by the use of patch tests with Asterol tincture, ointment, or dusting powder showed that in concentrations of 2 to 5%, Asterol was neither a primary irritant nor a powerful sensitizer. However, in a 10% concentration it caused local irritation in all of 10 patients patch-tested.[3] The percentage of inflammatory reactions of the scalp subsequent to the topical use of Asterol has ranged from 16.7 to 32.8%. This reaction is not undesirable, since rapid cure often follows in its wake.

In early 1952, two patients were admitted to the St. Louis Children's Hospital with neurological signs and symptoms and the history of having received topical applications of Asterol for the treatment of tinea capitis. However, a causal relationship to Asterol could not be established, and the personal and family history of convulsions in one case suggested that the association was probably coincidental.

The manufacturers of Asterol had received sporadic reports of neurological disturbances related with Asterol application, and, based upon these and our two cases, letters advising caution were distributed to physicians carrying on Asterol studies, and labels were affixed to the proprietary preparation warning that it not be used on infants.[6]

In view of the prevalence of tinea capitis and the reported advantages of Asterol over previously recommended antifungal agents, it appeared urgent to investigate further the neurotoxic properties of Asterol, if any.

METHODS

It was planned to do a neurological and electroencephalographic examination on each tinea capitis patient prior to treatment and at monthly or shorter intervals thereafter until treatment was concluded. For electroencephalograms eight scalp electrodes were used routinely with

Supported in part by a grant from Hoffmann-LaRoche, Inc., Nutley, N. J.

From the Departments of Pediatrics and Neuropsychiatry, Washington University School of Medicine, and the St. Louis Children's Hospital.

* References 1-5.

interconnected ear grounds. Bipolar combinations between neighboring electrodes were recorded upon an eight-channel Grass electroencephalograph, using a sensitivity of 6 to 8 mm. per 50 μv. Each recording lasted 24 minutes, and children old enough to understand the request were hyperventilated vigorously for 2 minutes followed by a 2-minute posthyperventilation record. In classifying the records we took into account maturation factors and allowed a significant latitude in interpreting the amount of slow activity which might appear in children of the same chronological age. No record was classified as slow that we did not believe to contain an excess after variability had been taken into account.

After the initial neurological examination and electroencephalogram, the parents were instructed to apply 5% Asterol ointment morning and night, using 2 oz. (60 gm.) weekly. The scalp was shaved or clipped closely once weekly and shampooed every second day. No instructions were given concerning the use or care of skull caps.

TABLE 1.—*Age of Patients Receiving Asterol Therapy*

Age, Mo.	No. Cases	Age, Mo.	No. Cases
Up to 12	..	73-84	7
13-24	1	85-96	4
25-36	2	97-108	5
37-48	..	109-120	5
49-60	5	121-132	..
61-72	6	133-144	1
		Over 144	1
		Total	37

TABLE 2.—*Character of Control Electroencephalograms Presenting Activity Outside the Normal Range for Age*

Character	No. Cases
Unstable due to marked HV build-up	2
Borderline slow	2
Some excess of slow for age	4
Definite excess of slow	1
Mixed slow and fast pattern	3
High voltage convulsoid spikes	2
Total	14

PRETREATMENT FINDINGS

To date, 57 patients in the tinea-capitis clinic have registered for the Asterol research program. Seven patients failed to return after preliminary electroencephalograms. Another 13 subjects are at present being followed actively. In the remaining 37 patients the age range was from 16 months to 12 years with an average of 6.7 years (Table 1). Fourteen patients were under 6 years of age, 8 were under 5, and 3 were under 4 years of age. Thirteen of the 37 patients were white, and 24 were Negroes. Thirty-five of the 37 patients were boys.

Two patients had a past history of one convulsion each. Six others gave a history of convulsive disorder in the immediate family or close relatives. In two the family history was unknown.

Since the age range of the children was 16 months to 12 years, a wide distribution of frequencies characterized the control records. Twenty-three children (62%) showed normal electroencephalograms prior to treatment with Asterol. Fourteen pretreatment electroencephalograms presented activity considered to be

outside the normal range for age (Table 2). Thus, a distribution including, as well as presumed normals, some subjects with personal or family history of convulsions and others with disordered pretreatment records of brain activity but without convulsions, was considered ideal for investigating any neurotoxic effects Asterol might have.

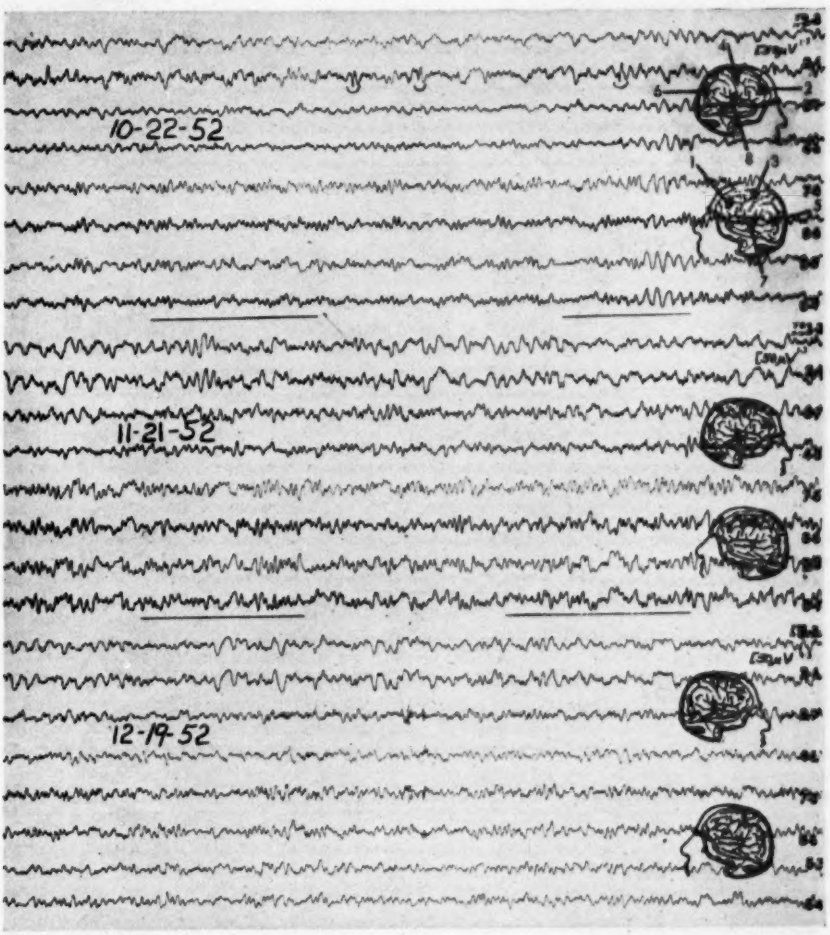

Chart 1.—Patient J. G.; pretreatment electroencephalogram presents a right frontotemporal spike.

POST-TREATMENT FINDINGS

Thirty-six patients have had Asterol applied to the scalp for at least 4 weeks and many for as long as 22 weeks, with an over-all total of 365.5 weeks and an average of 10.2 weeks of therapy. These 36 cases plus another who developed symptoms after 11 days of therapy are analyzed below.

In the 14 cases with pretreatment electroencephalograms considered to be outside the normal range for age, the duration of therapy extended from 4 to 19 weeks, with an average of 9.9 weeks. The two patients with known past history of a convul-

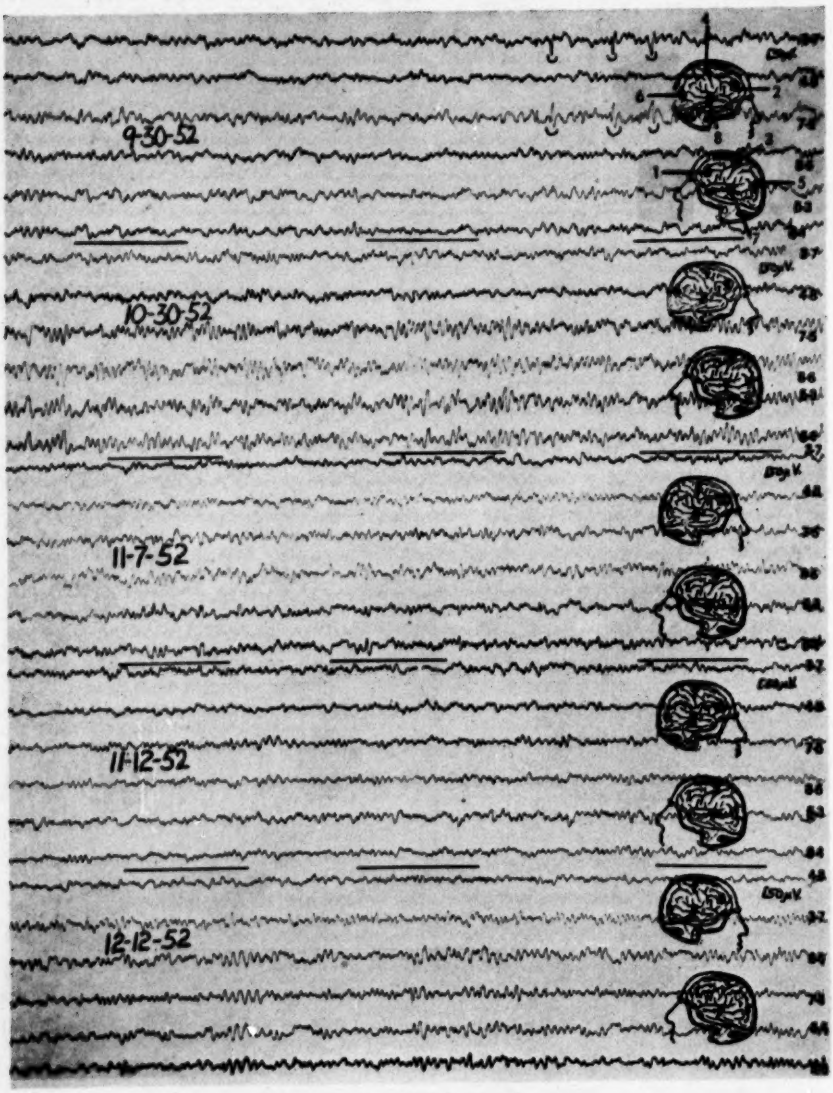

Chart 2.—Patient C. S., Case 1.

sion fell in this group, the one with a single febrile seizure exhibiting a slow but not disordered record, and the other (J. G.) who had experienced an afebrile seizure showing a right frontotemporal spike consistent with a convulsive etiology for it (Chart 1). In both of these cases cure was effected on 9 weeks of therapy and

without the development of abnormal clinical signs or symptoms or further change in the electroencephalogram. Likewise, all of the other patients, save for one, in this group with disordered control records failed to show clinical or further electroencephalographic abnormalities after treatment with Asterol. One patient in this group, C. S., who showed an abnormal control record with left midtemporal spikes (Chart 2) but who had not had seizures developed visual hallucinations 33 days after onset of therapy. This patient will be discussed subsequently under case reports (Case 1).

Of the 23 cases who showed records normal for age prior to the use of Asterol, one developed electroencephalographic changes without clinical symptoms (Case 2), and another showed hallucinations with electroencephalographic changes as outlined below (Case 3).

REPORT OF CASES

Following are descriptions of the three cases in which reactions occurred.

CASE 1.—C. S. (Chart 2), a 5 3/12-year-old Negro boy, was started on Asterol therapy on Sept. 30, 1952. There was a negative past and family history of convulsive disorder, and the complete physical examination was normal. The control electroencephalogram on Sept. 30, 1952, was well ordered save for a convulsoid spike which appeared intermittently in the left temporal region. It was decided to start Asterol applications but to keep the patient under close observation. A repeat electroencephalogram on Oct. 30, 1952, showed an unchanged record save for the absence of left temporal spikes noted earlier, and the tracing was regarded as normal for the age. Three days later, Nov. 2, 1952, four and one-half weeks after onset of therapy, the patient suddenly developed visual and tactile hallucinations. These episodes were recurrent, and in obvious terror he claimed to see on different occasions snakes, elephants, frogs, mice, pumpkins, and butterflies. He was observed picking unseen objects off his body and claimed his hands hurt him "from squeezing the snakes." No history of precipitating psychogenic factors could be elicited. He had attended a children's Halloween party two days previously in the mother's presence, at which time he appeared quite undisturbed, and no causal relationship could be determined. He was admitted to the St. Louis Children's Hospital on Nov. 3, 1952, at which time Asterol was discontinued. The physical examination was entirely negative. Exclusive of the hallucinations, he appeared well oriented and in full possession of all faculties. Electroencephalograms on Nov. 4, 1952, and Nov. 7, 1952, two and five days, respectively, after onset of symptoms, were interpreted as normal for age with no evident spikes. Lumbar puncture gave normal dynamics, cell count, and chemical determinations. He continued to have hallucinations with decreasing frequency for four days after admission, and over the ensuing five days he occasionally expressed fear of their return. On Nov. 12, 1952, five days after freedom from actual hallucinations, the electroencephalogram was repeated with normal findings, and Asterol was reapplied to the scalp. He was observed in the hospital for the next seven days on continued scalp medication and without recurrence of hallucinations or other untoward symptoms. He was discharged on Nov. 19, 1952, to be followed in the outpatient department and with instructions to continue Asterol. On Dec. 12, 1952, some four weeks after reapplication of Asterol, the neurological examination and electroencephalogram were again normal. He had been entirely free of hallucinations, but appeared to be afraid of the dark. A night light was placed in his room. On her own initiative, the mother discontinued Asterol on Dec. 22, 1952, because he complained of a transient "headache." He was last seen in the clinic on Jan. 20, 1953, at which time he still showed fluorescent hairs under the Wood's light, but the mother declined further treatment.

CASE 2.—R. L. (Chart 3), a 4½-year-old Negro boy, was started on Asterol therapy (instructions for use as previously outlined, using 2 oz. of Asterol weekly) on April 22, 1952. There was a negative personal and family history for convulsive disorder, and the neurological examination was usual. The control electroencephalogram of April 22, 1952, was considered to be within normal limits. It showed a 7- to 9-per-second basic resting occipital frequency. There was also some 4- to 6-per-second activity exaggerated by hyperventilation. The first

repeat record (May 22, 1952) after 30 days of Asterol applications was similar, but sleep sequences showed sporadic temporal spikes as well as 12-per-second spindles and irregular 4- to 6-per-second activity. This was interpreted as a nonfocal dysrhythmia, but since the tracing included sleep sequences, comparison with the original waking control of April 22, 1952,

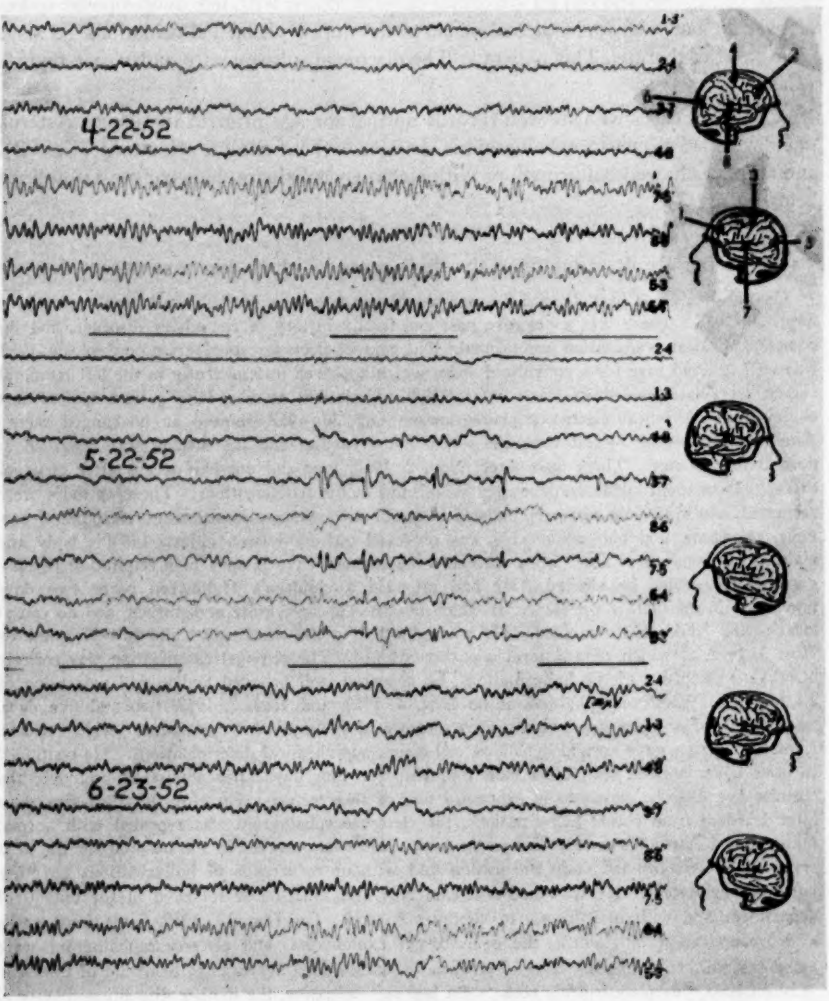

Chart 3.—Patient R. L., Case 2.

was considered equivocal. Asterol was discontinued on May 22, 1952. Six days later, on May 28, 1952, a repeat waking record showed the original 7- to 8-per-second basic resting occipital frequency with scattered 5- to 6-per-second activity and a few temporal spikes, more commonly on the left. A repeat electroencephalogram on June 23, 1952, four and one-half weeks after discontinuation of Asterol, showed an 8- to 9-per-second basic resting occipital frequency with some 5- to 7-per-second activity and no evidence of spikes. That record was considered normal for the age of 4½ years. An electroencephalogram on Sept. 25, 1952, 18

weeks after the original spike record, was also normal for the age. Throughout all of these visits, the patient remained subjectively and objectively asymptomatic, and the possibility that the midtemporal spikes had simply not been recorded in the control electroencephalogram was certainly not excluded.

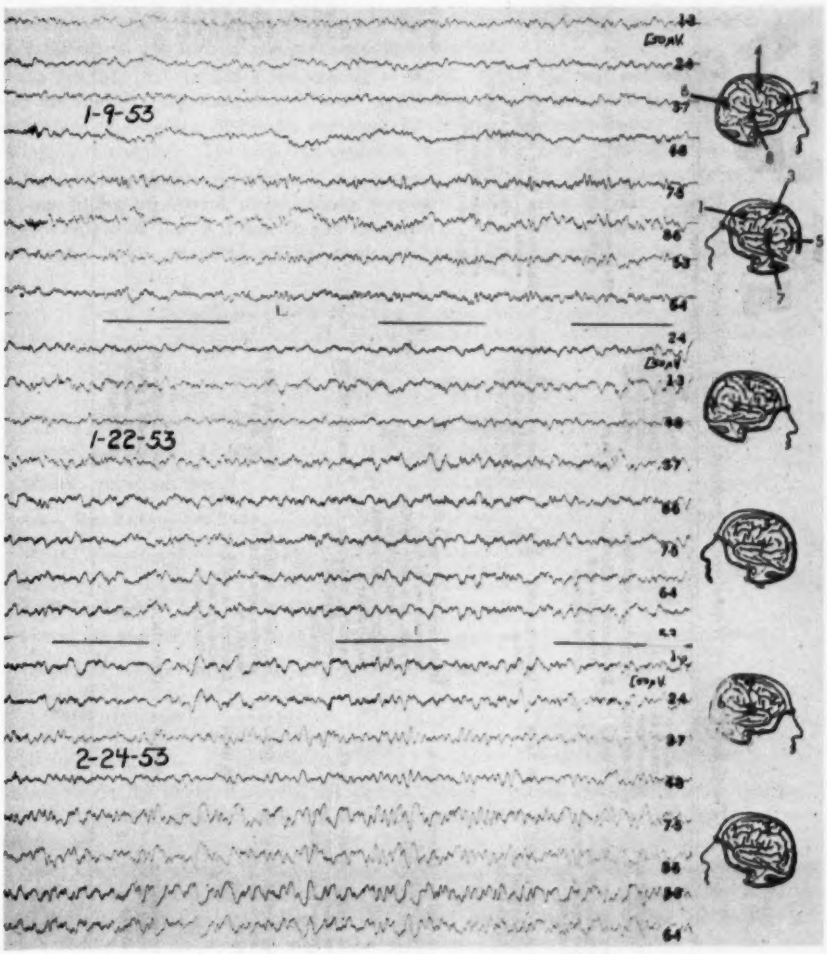

Chart 4.—Patient J. S., Case 3.

CASE 3.—J. S. (Chart 4), a 4 10/12-year-old Negro boy, was first seen in the tinea capitis clinic on Jan. 9, 1953. The past history was negative and physical and neurological examinations normal. A pre-Asterol electroencephalogram on that day showed a relatively low voltage, a somewhat choppy record without focal signs or paroxysmal activity which was interpreted as normal for the age. Eleven days after starting therapy (Jan. 20, 1953) the patient had a sudden onset of visual hallucinations—frequent recurrent episodes of screaming and claiming to see snakes and insects. There were no convulsive movements, and between the hallucinatory episodes he appeared and acted normal. He was admitted to the St. Louis Children's Hospital on Jan. 21, 1953, at which time Asterol was discontinued. Physical examination was normal.

TABLE 3.—*Published Cases of Neurotoxic Symptoms Related to Asterol Therapy*

Authors	Case No.	Age, Race, Sex	Diagnosis and Treatment	Duration of Therapy at appearance of Symptoms	Symptoms and Signs	Duration of Symptoms After Discontinuation of Asterol	EEG	Follow-Up
Wilson, Levitt, Harris, and Hellgman [9]	4	4 yr., M	Tinea capitis; tinea corporis; 5% tincture and 5% Asterol ointment	9 days	Disoriented, hallucinations, tonic and clonic tremors	6 days	Hypersynchronous 6/sec. waves, nonfocal	6 days after symptoms disappeared Asterol tincture reapplied; two days later hallucinations and disorientation reappeared; Rx stopped; symptom-free in 4 days
	5	10 wk., F	Monilia dermatitis; 2½% Asterol dihydrochloride	26 days	Lethargy and convulsions	Free of convulsions and twitchings by fifth day	Paroxysmal large spikes—nonfocal—in otherwise normal record; repeat EEG on 7th hospital day; sharp waves replaced spikes—record improved	.....
Hitch [9]	1	2½ yr., W, M	Tinea capitis; Asterol tincture (up to 6 oz. [187 gm.] daily!)	1 wk.	Hallucinations, clonic convulsions of face, hands, and feet; rolling eyes; dazed; rotary nystagmus; increased deep reflexes	1 wk.	.....	Recovered
	2	4½ yr., W, M (emotionally unstable)	Tinea capitis; excessive amount tincture and ointment	8 wk.	Dysarthria, weakness, incoordination, vomiting	Cleared rapidly	.....	5 mo. later further evidence of original behavior disturbance evident prior to Asterol therapy
	3	3 yr., W, M	Tinea capitis; Asterol tincture and ointment	53 days 68 days	Convulsion, lethargy; physical examination negative Another convulsion; lethargy and hallucinations	Symptom-free in 10 days	.....	3 mo. later, history, physical examination, laboratory, and x-ray studies negative; EEG few bursts enlarged slow and fast waves, nonfocal; pattern interpreted as within normal limits; 3 mo. later normal progress
Featherston [10]	6	4 mo.	Tinea corporis; Asterol dihydrochloride	10 days	Convulsions	Convulsions continued 2 days after cessation of Asterol	.....	No further convulsions

Lumbar puncture revealed normal pressure and normal cell count and chemical determinations. An electroencephalogram on the day after admission, Jan. 22, 1953, contained more irregular slow activity than had been evident at the earlier recording and was of higher voltage. It was suggestive of mild dysrhythmia. The frequency of hallucinations decreased rapidly after admission, and they were entirely gone within 72 hours of admission.

He was observed without therapy until Jan. 29, 1953, at which time Asterol was reapplied. An electroencephalogram on this date showed significantly more normal resting frequency, and the incidence of slow activity was correspondingly reduced.

On Jan. 31, 1953, he had a temperature of 38.8 C. (101.8 F.) and vomited once. On the next day, Feb. 1, 1953, there was evidence of Koplik's spots in his mouth and a papular rash on his face. A diagnosis of rubeola was made (there was a history of recent exposure to two siblings with rubeola). The rash thus appeared 13 days after onset of hallucinations.

He was kept under observation in the hospital until Feb. 9, 1953. During these 11 days of reapplication of Asterol, there were no untoward clinical signs or symptoms. An electroencephalogram on Feb. 9, 1953, the day of discharge, showed an increase in slow activity as compared with the preceding one and moderate hyperventilation build-up, but was still con-

TABLE 4.—*Published Series of Tinea Capitis Cases Treated with Asterol*

Authors	No. Cases Tinea Capitis	Form of Asterol in Treatment	Duration of Asterol Therapy
Stritzler, Fishman, and Laurens [4]	77	2% tincture 2% ointment	1-16 wk.
Stritzler, Fishman, and Laurens [9]	19	5% tincture 5% ointment	Up to 12 wk.
Edelson, Craster, and Haskin [8]	72	2 and 5% tincture and ointment	2-17 wk.
Appel, Tye, Halpern, and Paci [11]	61	2% tincture 2% ointment	31 cases less than 3 mo. 30 cases more than 3 mo.
Ravits [12]	6	5% tincture and ointment	1-5 mo.
Snyder [13]	60	5% ointment	1-12 mo.
Edelson and Haskin [14]	61	5% ointment 5% tincture	3-21 wk.
Sullivan and Bereston [15]	103	2% ointment	At least 3 mo. if not cured earlier
Slaughter [16]	11	5% tincture 5% ointment	6 wk.-4 mo.
Total	470		

sidered within the limits of normal for age of patient. Asterol applications were continued until Feb. 24, 1953, at which time the scalp was free of fluorescent hairs, and treatment was discontinued.

Since hospital discharge, he had remained asymptomatic, except on only one occasion when he woke up at night crying and insisted that his mother stay by his side. There were no hallucinations or other evident causes for this solitary disturbance. Since then his mother has kept a light on in his room at night. An electroencephalogram on the day treatment was discontinued showed a definite increase in 2- to 3-per-second slow activity with lessened incidence of basic frequency without hyperventilation build-up.

This child had two siblings, aged 17 months and 4 years, who concomitantly received Asterol treatment for tinea capitis and who developed no symptoms or electroencephalographic changes from the onset of therapy to cure, six and one-half weeks later. During the course of treatment they both developed uncomplicated rubeola.

COMMENT

Prior to the release of Asterol for clinical use, 746 cases of tinea capitis had been treated with Asterol without any effect on the central nervous system. Subsequently,

Asterol was used for approximately three months in over 800 children afflicted with tinea capitis in Sault Ste. Marie, Ont., Canada. In none of these instances were any effects on the nervous system reported.[6]

An attempt was made to determine the incidence of neurotoxicity by reviewing all published series of tinea capitis treated with Asterol (Table 4). The collected reports are comprised of 470 children treated with Asterol from one week to one year, without mention of neurological disturbances. These reported cases of tinea capitis treated with Asterol must obviously represent but a part of all the children who have received Asterol for fungus infections of the scalp or elsewhere on the body.

Subsequent to the beginning of our study, reference to possible neurotoxicity of Asterol was first reported by Stritzler [7] as follows.

> Toxic reactions may very rarely occur in young children following excessive use of tincture of Asterol on the scalp, with symptoms of hallucinations, convulsions, and ataxia. These subside in a few days when therapy is discontinued, leaving no sequelae. We have seen this reaction in one patient of about 500, but have heard of two similar cases, one in North Carolina and another observed by Irving Fishman of Jamaica, New York.

The three cases referred to by Stritzler have recently been published by Hitch.[9] In addition, there have been reported in the literature two patients with central-nervous-system disturbances by Wilson and co-workers [8] and one by Featherston.[10] Table 3 summarizes all published cases of neurotoxic symptoms evident during the course of topical Asterol therapy.

Pertinent to this problem is the incidence of neurotoxicity, causal or otherwise. Stritzler [7] found this in about one out of 500 patients. Wilson and co-workers [8] estimated an incidence of less than 1 per 1,000 children treated. Pirk and Sevringhaus,[6] by taking into consideration all of the reports of neurotoxicity which they have received and without excluding those situations in which a causal relationship to Asterol can be ruled out or which represent quite unusual problems, have calculated that the incidence of central-nervous-system reactions following the use of Asterol is 0.0125%. This is based on the estimate that through 1952 over 300,000 patients have used Asterol.

In one case of neurotoxicity due to Asterol reported by Wilson and co-workers,[8] the toxic symptoms recurred when therapy with Asterol was reinstituted. We were unable to observe renewed evidence of toxicity in our cases when Asterol was again applied following an initial reaction.

The group selected in our program proved insufficient in size to demonstrate conclusively if Asterol has neurotoxic properties. However, the findings point up the necessity of considering several significant factors in future studies and thus are worthy of report as preliminary results. Convulsions did not develop in any instance, but in two patients tactile and visual hallucinations appeared during the course of the applications. These disappeared when the applications were stopped and did not recur when treatment was reinstituted. In neither of the cases was there objective evidence of neurological disturbance, and the electroencephalograms of the two remained relatively unchanged during the hallucinatory period. In one, family and personal history was negative for convulsive disorder, but a midtemporal focal spike (such as may be seen in child convulsives) was recorded intermittently

during the pretreatment electroencephalogram. The other child had a negative family and personal history, and the control electroencephalogram, as well as the treatment ones, was within the range of normal variability.

Finally, in a third child, also with negative personal and family convulsive history, a paroxysmal midtemporal focal spike first appeared during the applications, but there were no associated clinical manifestations. Since midtemporal spikes may be inconstant in the successive records of known convulsives, there is the definite possibility that the spike had been latent at the initial recording and appeared later as a chance finding unrelated to the Asterol applications.

This preliminary report indicates the importance of pretreatment electroencephalograms if convulsive manifestations which appear in children under Asterol treatment are to be evaluated conclusively. In two presumed normals of this series, paroxysmal spikes were recorded in pretreatment records. Only one of these had a personal convulsive history (one febrile convulsion). This chance variability in a control group selected for treatment because of tinea capitis infection indicates to us the importance of more extensive studies if the neurotoxic properties of Asterol are to receive a thorough evaluation. We are now enlarging our series to obtain such information.

SUMMARY

Electroencephalograms were obtained before, during, and after Asterol therapy in 37 cases of tinea capitis.

The incidence, 38%, of pretreatment electroencephalograms with activity outside normal range for age indicates the need of controls in the evaluation of convulsive symptoms.

Two children developed hallucinations during therapy; reexposure to Asterol failed to duplicate these episodes. Another child had electroencephalographic changes without clinical symptoms. There is the possibility that the electroencephalographic spike had been latent at the initial recording and appeared later as a chance finding unrelated to the Asterol applications.

ADDENDUM

Subsequent to the preparation of this report, two siblings (age 2½ and 4½ years) have shown significant electroencephalographic changes after one and two months of Asterol treatment, respectively, with vague evanescent symptoms and negative clinical findings. In one there was a history of the child's sucking his Asterol-impregnated skull cap. These cases were followed without Asterol until the electroencephalograms had returned to the original patterns. Asterol was then reapplied for two and one-half months in each case without clinical symptoms or significant electroencephalographic changes. Both children were cured of tinea capitis.

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TREATMENT OF TUBERCULOUS MENINGITIS

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THIS REPORT presents the results of the treatment of two series of infants and children with tuberculous meningitis. The first, consisting of 19 patients, was treated from May, 1947, to February, 1952, with use of a regimen of intramuscular and intrathecal streptomycin, plus oral paraaminosalicylic acid and/or thiazolsulfone (Promizole). The current series of six patients has been treated since May, 1952, with the use of a regimen of intramuscular streptomycin and oral paraaminosalicylic acid and isoniazid, without intrathecal streptomycin. Serum and cerebrospinal fluid isoniazid levels and other laboratory studies are included for the first three patients of the second series and for a fourth patient with only miliary tuberculosis, who served as a control.

Success in the treatment of tuberculous meningitis has been attained by various regimens. Lincoln and co-workers,[1] in 1948, reported one of the most favorable early series, with six surviving out of seven patients, using intramuscular and intrathecal streptomycin and oral thiazolsulfone. Using streptomycin alone, Cairns, Smith, and Vollum,[2] in 1950, obtained good results in 56% of 93 patients, many of whom were adults. Flori,[3] reporting studies carried out under the guidance of Cocchi, in 1950 had achieved success in a similar percentage of 265 children and young adults with streptomycin and intravenous sodium glucosulfone (Promin). Using streptomycin combined with paraaminosalicylic acid and/or thiazolsulfone, Alexander [4] reported survival of 48% of 93 infants and children treated by a cooperative group under the auspices of the National Institutes of Health. Clark and co-workers [5] have presented encouraging evidence in favor of the combination of intramuscular streptomycin and oral isoniazid. Morin [6] noted improvement in two adults and three children treated with isoniazid alone. Lincoln [7] recently has reported that her series has been increased to 52 patients, with an over-all survival of 67%; however, she has shown that the percentage can be as high as 91% if therapy is started in the first stage of the disease. Isoniazid recently has been added to her original regimen.

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TABLE 1.—*Series Treated with Intrathecal Streptomycin*

Patient	Race, Sex	Age	Ill Before Admission	Status on Admission	Tbcln.	Acid-Fast Organisms Found in C. S. F.	Chest X-Ray	Treatment*					Result
								Intramuscular		Intrathecal	Oral		
								SM Daily Dose, Duration	DHSM Daily Dose, Duration	SM Dose, No.	TZSE Daily Dose, Duration	PAS Daily Dose, Duration	
Eight Surviving Patients													
GWC	W, M	6 mo.	3 wk.?	Meningeal irritation	Pos.	Pos.	Tuberculous pneumonia	1.0 gm., 3 mo.	.....	50 mg., 48	.....	.....	Mental deficiency and hydrocephalus
JWT	W, M	2½ yr.	1 wk.?	Semicomatose	Pos.	Pos.	Neg.	0.4-0.9 gm., 6 mo.	.....	50 mg., 45	1.0 gm., 14½ mo.	.....	Mental deficiency
FJB	W, F	9 mo.	10 days	Early meningeal irritation; hemiparesis	Pos.	Pos.	Miliary	0.9 gm., 6 mo.	.....	50 mg., 40	1.0-1.5 gm., 26½ mo.	.....	Neurological defect
WAP	W, M	4 mo.	1 wk.	Meningeal irritation	Pos.	Neg.	Primary	0.9 gm., 6 mo.	.....	50 mg., 22	1.0-1.5 gm., 28½ mo.	.....	Good; arrested hydrocephalus; relapse 22 mo. after discharge
			2 wk.	Semicomatose	....	Pos.	Primary	1.0 gm., 4 mo.	.....	100 mg., 40	1.0-2.0 gm., 4 mo.	2.0 gm., 4 mo.	Good
RCM	W, F	16 mo.	2 wk.	Semicomatose	Pos.	Pos.	Miliary	1.0 gm., 1 mo.	1.0 gm., 4 mo.	50 mg., 30	1.0-2.0 gm., 5½ mo.	.....	Good; relapse 3 wk. after discharge
			1 wk.	Early meningeal irritation	....	Pos.	Calcified primary	.....	1.0 gm., 5½ mo.	50 mg., 21	1.6 gm., 17 mo.	.....	Good; treatment completed at home
JDR	W, M	8 mo.	8 days?	Early	Pos.	Neg.	Miliary	0.5 gm., 5 mo.	.....	50 mg., 21	1.0 gm., 2 mo.	.....	Good; treatment completed at home
JWF	W, M	2 yr.	2 wk.	Meningeal irritation	Pos.	Pos.	Primary	0.5 gm., 4⅔ mo.	0.5 gm., 1⅔ mo.	50 mg., 20	1.0 gm., 24 mo.; still receiving	2.0 gm., 16 mo.	Good; treatment completed at home
CJC	N, M	14 mo.	1 wk.	Meningeal irritation	Pos.	Neg.	Miliary	0.5 gm., 2 mo.	.....	50 mg., 40	2.0 gm., 2 mo.	3.2 gm., 2 mo.	Mental deficiency
Eleven Deceased Patients													
DB	W, M	6 yr.	5 days?	Meningeal irritation	Pos.	Neg.	Neg.	0.5-1.6 gm., 2 mo.	.....	100 mg., 39	.....	.....	No response to Rx; autopsy: TB meningitis with caseation left cerebrum
WHM	W, M	9 yr.	10 days	Early meningeal irritation	Pos.	Pos.	Miliary	0.5-1.0 gm., 2 mo.	.....	None	.....	.....	Inadequate treatment; no autopsy
BM	N, F	2½ yr.	3 wk.	Terminal	Neg.	Pos.	Calcified primary	0.9 gm., 2 doses only	.....	50 mg., 1	.....	.....	Terminal on admission; no autopsy

JEW	N, M	3 yr.	2 wk.	Terminal	Pos.	Pos.	Neg.	0.9 gm., 1 day	.....	50 mg., 2	.....	.....	Terminal on admission; no autopsy
SJT	W, F	2 yr.	2 wk.	Comatose	Neg.	Pos.	Miliary	.....	1.0 gm., 4 mo.	50 mg., 28	1.0-3.0 gm., 6 mo.	.....	Mental deficiency and hydrocephalus; died at home; no autopsy
IB	N, F	14 mo.	5 days	Meningeal irritation	Pos.	Pos.	Primary	.....	0.5 gm., 4 mo.	50 mg., 20	1.0-2.0 gm., 4½ mo.	.....	Early relapse; no autopsy
JAS	W, F	18 mo.	2 wk.	Semicomatose	Pos.	Pos.	Primary	.....	0.5 gm., 4 mo.	50 mg., 20	1.0-3.0-gm., 15 mo.	.....	Blind rt. eye; right hemiparesis; 1st relapse 11 mo. after discharge
			2 wk.	Early meningeal irritation; paralyses	....	Neg.	Calcified primary	.....	0.7 gm., 6 mo.	50 mg., 40	1.5-2.0 gm., 10½ mo.	2.0 gm., 6 mo.	Improved; treatment completed at home; 2d relapse 3 wk. after treatment stopped
			2 wk.	Early meningeal irritation; paralyses	....	Pos.	Calcified primary	1.0 gm., 2 mo.	.....	100 mg., 40	2.0 gm., 2 mo.	2.0 gm., 2 mo.	Improved; not treated at home; 3d relapse 7 wk. after discharge
			2 wk.	Early meningeal irritation; paralyses	....	Pos.	Calcified primary	.....	.....	.....	.....	.....	Late relapse; died; autopsy: TB meningitis with hydrocephalus
JAC	W, F	1 yr.	1 wk.	Early	Pos.	Pos.	Primary	.....	1.0 gm., 4 mo.	50 mg., 21	1.5 gm., 5 mo.	.....	Improved; treatment completed at home; relapse 5 wk. after treatment stopped
			3 days	Early meningeal irritation	....	Pos.	Primary	.....	0.5 gm., 1 mo.	50 mg., 20	1.0 gm., 3 mo.	.....	Late relapse; died at home; no autopsy
LAC	W, M	3 yr.	6 wk.?	Early	Pos.	Pos.	Primary	.....	0.5 gm., 2⅔ mo.	50 mg., 20	1.5 gm., 2½ mo.	.....	No response to Rx; autopsy: TB meningitis with hydrocephalus
RB	N, M	1 yr.	12 days	Comatose	Pos.	Neg.	Neg.	0.2 gm., 10 days	0.5 gm., 11 days	50 mg., 7	1.0 gm., 11 days	2.0 gm., 7 days	Inadequate Rx; autopsy: TB meningitis with hydrocephalus
PLD	W, F	4 mo.	4 wk.?	Meningeal irritation	Neg.	Pos.	Miliary; tuberculous pneumonia	0.5 gm., 14 days	.....	50 mg., 9	1.0 gm., 14 days	1.4 gm., 14 days	No response to Rx; autopsy: TB meningitis and pneumonia; miliary tuberculosis; hydrocephalus

* SM indicates streptomycin; DHSM indicates dihydrostreptomycin; TZSE indicates thiazolsulfone (Promizole); PAS indicates paraaminosalicylic acid.

SERIES TREATED WITH INTRATHECAL STREPTOMYCIN

The first series of 19 patients, treated from May, 1947, to February, 1952, reflects the progress of treatment during that period. Complete data on these patients are shown in Table 1 and are summarized in Table 2.

The regimen of treatment varied with the current trends and the availability of new drugs, but in general it consisted of intramuscular streptomycin or dihydrostreptomycin, 20 to 50 mg. per kilogram of body weight per day, in divided doses every 12 hours, for at least six months; intrathecal streptomycin, 50 to 100 mg. per day, for about 40 injections in about six to twelve weeks, or until the cerebrospinal fluid was normal; oral thiazolsulfone, 1 to 3 gm. per day (in an effort to obtain a blood level of 1 to 3 mg. per 100 cc. of blood about 3 hours after administration of the drug), in divided doses every 6 hours, for six months to three years, and of oral paraaminosalicylic acid, 0.2 gm. per kilogram of body weight per day, in divided doses every 6 hours, for six months or longer.

TABLE 2.—*Summary of the Data on the Patients in the First Series, as of February, 1952*

Total patients treated	19
Number surviving	8
Number deceased	11
% surviving	42%

TABLE 3.—*Status of the Eight Surviving Patients in the First Series, as of February, 1952*

Mentally defective	3
Residual neurological defect	1
Good condition (relapse with recovery—2)	4
Longest survival	
Mentally defective	4½ yr.
Good condition	4 yr.

Reactions to the drugs were not common. Transient vestibular dysfunction was definite in one patient and transient deafness in two. One had a temporary maculopapular skin eruption, and several had slight eosinophilia. No toxicity due to thiazolsulfone was noted, possibly because of the small doses used. The principal toxic disturbance was from intrathecal streptomycin, which frequently seemed to produce vomiting, convulsions, high fever, nystagmus, and stupor, as well as increased cerebrospinal fluid protein and cell content. One patient received four intrathecal doses of 30,000 to 50,000 units of streptokinase-streptodornase mixture, but because of the violence of his reaction, the treatment was not continued.

Eight patients (42%) survived, but of these only four were without mental or neurological defects (Table 3). Of the four in good condition, two were treated once each for relapse. The longest survival, as of February, 1952, was four and one-half years for a mentally defective patient and four years for a patient in good condition. Of those who survived, only one was of the Negro race.*

* Patient 8, C. J. C., the only surviving Negro, died at home on March 24, 1952, of an apparent respiratory infection, approximately two months after the completion of this data. His death reduced the percentage surviving to 37.

Eleven patients died (Table 4), four of whom were of the Negro race. Of eight who died in less than six months, two were in a terminal condition on admission and died in less than one week, two received inadequate treatment, three showed no response to treatment and died on the 14th, 80th, and 87th hospital days, and one had early relapse after adequate treatment and died on the 145th hospital day. Of three who died more than six months after the onset of their illness, one developed hydrocephalus with mental deficiency in spite of apparently adequate treatment and died at home one year after the onset of her illness, and two died with late relapse, one having had two courses of retreatment and one having had one course of retreatment.

All but two had definite household exposure to known cases of tuberculosis. All but four were proved bacteriologically by smear, culture, and/or guinea pig inoculation of cerebrospinal fluid. Of the four exceptions, two had characteristic findings at postmortem examination, one had associated miliary tuberculosis and developed bacteriologically proved tuberculosis of the hip with abscess one year after completing treatment, and one was unproved, although all of the other features of his illness were typical.

TABLE 4.—*Status at Time of Death of the Eleven Deceased Patients of the First Series*

Early death (under 6 mo.)	8
Terminal on admission	2
Inadequate treatment	2
No response to treatment	3
Early relapse	1
Late death (over 6 mo.)	3
Complications	1
Late relapse	2

Patients with associated miliary tuberculosis or tuberculous pneumonia had no apparent poorer prognosis than those without these pulmonary manifestations. Roentgenograms of the chest showed that miliary tuberculosis and tuberculous pneumonia cleared promptly in two to five months.

SERIES TREATED WITHOUT INTRATHECAL STREPTOMYCIN

The second series of six patients is small, and the patients have been observed for only a short period of time. Nevertheless, it presents a striking contrast to the first series. Data on these patients are shown in Table 5.

The present regimen of treatment consists of intramuscular streptomycin, 40 mg. per kilogram of body weight per day, but not more than 1.0 gm., in one dose, daily until the clinical course and cerebrospinal fluid are normal, and then three times weekly, for a total course of at least 6 months; oral paraaminosalicylic acid, 0.2 to 0.4 gm. per kilogram of body weight per day, in divided doses three times daily, for at least 12 months, and oral isoniazid, 5.0 mg. per kilogram of body weight per day, in divided doses every 12 hours, for at least 12 months. This schedule is outlined in Table 6. None of the reported toxic manifestations was detected.†

† References 8 and 9.

TABLE 5.—*Series Treated Without Intrathecal Streptomycin*

Patient	Race, Sex	Age	Ill Before Admission	Status on Admission	Tbcln.	Acid-Fast Organisms Found in C. S. F.	Chest X-Ray	Treatment: Intramuscular Streptomycin, Daily Dose, Duration	Treatment: Intramuscular Streptomycin, 3 Times Weekly Dose, Duration	Treatment: Oral, PAS Daily Dose, Duration	Treatment: Oral, Isoniazid Daily Dose, Duration	Result
Four Surviving Patients												
DVW	N, F	11 mo.	1 wk.?	Meningeal irritation; posteonvulsive hemiparesis	Pos.	Pos.	Miliary	0.3-0.35 gm., 1½ mo.	0.3 gm., 8 mo.	1.5 gm., 12½ mo.; still receiving	40 mg., 12½ mo.; still receiving	Good; treatment continued at home
AOD	W, M	18 mo.	10 days?	Irritability and staggering gait	Pos.	Pos.	Primary?	0.5 gm., 2 mo.	0.5 gm., 7 mo.	1.5-2.25 gm., 12½ mo.; still receiving	60 mg., 12½ mo.; still receiving	Good; treatment continued at home
REP	W, M	4 yr.	10 days	Meningeal irritation	Pos.	Pos.	Neg.	0.5 gm., 3 mo.	0.5 gm., 4 mo.	3.0 gm., 11 mo.	80 mg., 11 mo.	Good; treatment completed at home
SOS*	W, M	20 mo.	2 wk.	Meningeal irritation	Pos.	Neg.	Primary	1.0 gm., 5 mo.	0.5-1.0 gm. 3½ mo.	3.0 gm., 9 mo.; still receiving	100 mg., 9 mo.; still receiving	Good; treatment continued at home
Two Deceased Patients												
SLG	N, M	16 mo.	2½ wk.	Meningeal irritation	Pos.	Pos.	Neg.	0.5 gm., 3 mo.	0.5 gm., 2½ mo.	1.5-2.25 gm., 7½ mo.	50 mg., 7½ mo.	Spastic paralysis and hydrocephalus; died at state hospital; no autopsy
GWC	W, M	20 mo.	10 days?	Terminal	Pos.	Pos.	Miliary	0.5 gm., 3 days	.....	1.0 gm., 3 days	50 mg., 3 days	Terminal on admission; no autopsy

* Data provided by Dr. Frank W. Gearing Jr., Woodstock, Va., who treated this patient under our guidance.

Four patients are alive and are in remarkably good condition. One of these has completed the course of treatment, and three are still receiving treatment.‡ There have been no relapses. The longest survival, as of May 15, 1953, is 12½ months. Data on the early cerebrospinal fluid response of these patients are shown in Charts 1 through 4.

Two patients died. One was in a terminal condition on admission and died after only three days of treatment, and one developed hydrocephalus with spastic paralysis

TABLE 6.—*The Present Regimen of Treatment for Tuberculous Meningitis*

Drug	Route	Daily Dose	Schedule	Duration of Administration
Streptomycin	Intramuscular	40 mg./kg.; not over 1.0 gm.	Daily	Until clinical course and cerebrospinal fluid are normal
			3 times weekly	For total course of at least 6 mo.
Paraminosalicylic acid	Oral	0.2-0.4 gm./kg.	3 times daily	For at least 12 mo.
Isoniazid	Oral	5.0 mg./kg.	Divided every 12 hr.	For at least 12 mo.

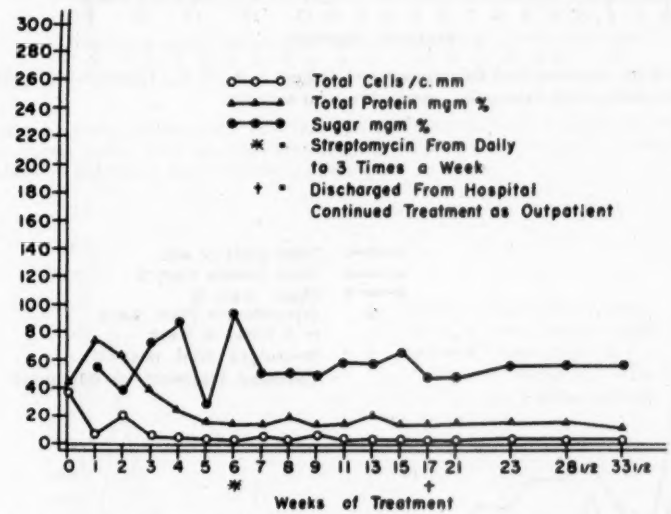

Chart 1.—Early cerebrospinal fluid response of Patient 1, D. V. W., 11-month-old Negro girl of the current series, with miliary tuberculosis and tuberculous meningitis, who survived.

and died at a state mental hospital eight months after the onset of illness, in spite of adequate treatment. Data on the early cerebrospinal fluid response of the second patient are shown in Chart 5.

All but one were proved bacteriologically by culture of cerebrospinal fluid. The exception otherwise had typical disease.

Roentgenograms of the chest again showed that associated miliary tuberculosis cleared promptly in about three months.

‡ As of June 30, 1953, three patients have completed all treatment, and one is still receiving paraaminosalicylic acid and isoniazid. All are in good condition.

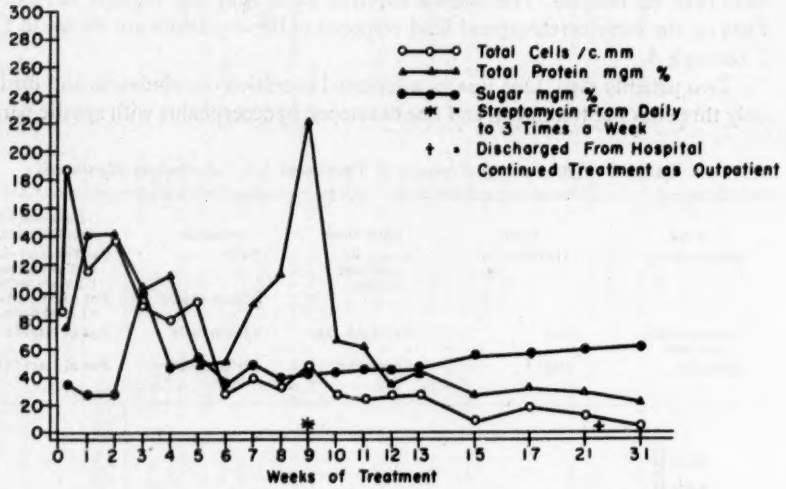
Total Cells /c.mm
Total Protein mgm %
Sugar mgm %
* • Streptomycin From Daily to 3 Times a Week
† • Discharged From Hospital Continued Treatment as Outpatient
Weeks of Treatment

Chart 2.—Early cerebrospinal fluid response of Patient 2, A. O. D., 18-month-old white boy of the current series, with tuberculous meningitis, who survived.

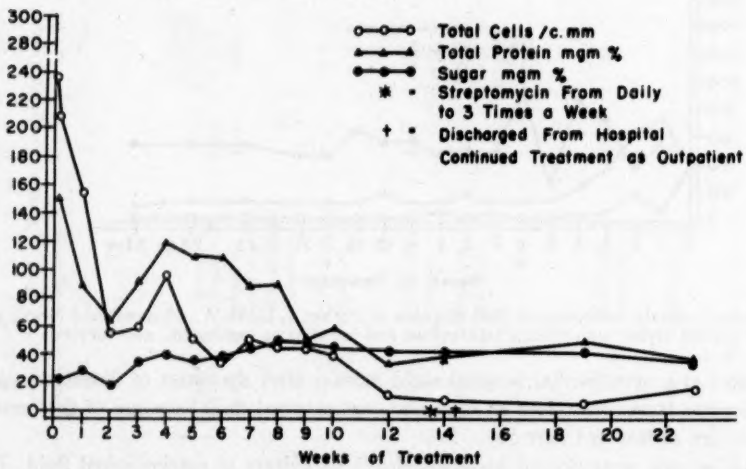
Total Cells /c.mm
Total Protein mgm %
Sugar mgm %
* • Streptomycin From Daily to 3 Times a Week
† • Discharged From Hospital Continued Treatment as Outpatient
Weeks of Treatment

Chart 3.—Early cerebrospinal fluid response of Patient 3, R. E. P., 4-year-old white boy of the current series, with tuberculous meningitis, who survived.

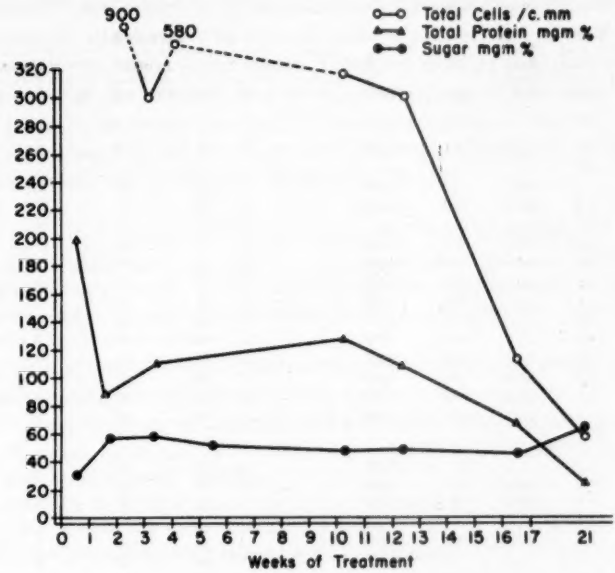

Chart 4.—Early cerebrospinal fluid response of Patient 4, S. O. S., 20-month-old white boy of the current series, with tuberculous meningitis, who survived. All of the components of the cerebrospinal fluid have since returned to normal.

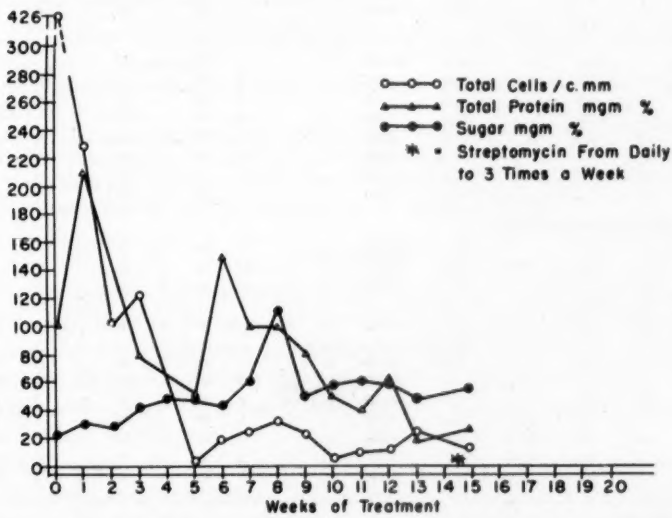

Chart 5.—Early cerebrospinal fluid response of Patient 5, S. L. G., 16-month-old Negro boy of the current series, with tuberculous meningitis, who died eight months after the onset of illness.

TABLE 7.—*Data on Serum and Cerebrospinal-Fluid Isoniazid Levels and Additional Laboratory Studies*

Date, 1962	Hr. Since Last Dose Isoniazid	Isoniazid Level Serum, γ/Ml.	Isoniazid Level C. S. F.* γ/Ml.	Sed. Rate (Bray), MM.	Hb.	WBC	Differential PMN M	PMN J	PMN B	PMN S	Lymphs LL	Lymphs SM	Mono. Lg	Mono. Tr	Mono. E	Mono. B	Levinson Test
Patient No. 1 (D. V. W.)																	
4/30	Admission	...	...	....	8.5	17,000	2	3	10	51	..	29	..	5	..	..	...
5/13	10	1.6	1.6	....	....	.....	..	..	..	..	..	..	..	..	..	..	3/1
5/14	7.5	0.3	...	15/5	7.5	9,500	..	..	11	55	..	23	..	5	3	..	...
5/20	9	3.1	1.5	20/—	9.0	26,500†	1	..	10	26‡	..	27	..	14	..	..	3/1
5/27	9	4.6	2.2	....	....	.....	..	..	3	42	..	37	2	12	..	..	2/1
6/ 3	1	1.8	0.9	28/—	9.0	21,200†	..	..	6	69	..	20	..	..	1	..	1/1
6/10	1.5	1.8	0.8	18/—	10.0§	10,500	..	..	12	52	..	33	..	2	..	..	1/1
6/17	1	...	0.1	....	9.5§	10,400	..	..	2	54	..	24	..	10	9	..	2/1
6/26	2.5	2.2	1.1	....	10.5	5,200	..	..	1	33	1	54	..	9	2	..	3/1
7/ 1	5	1.4	0.3	....	11.5	8,400	..	..	2	15‖	5	55	..	7	9	..	2/1
7/ 8	1.5	0.3	0.2	....	10.5	7,700	..	..	..	45	..	48	..	3	4	..	1/1
7/15	6	1.0	0.1	....	10.5	9,300	..	..	5	39	1	64	..	1	..	..	1/1
7/22	3	2.7	1.7	10/10	9.5	8,300	..	..	5	39	..	51	..	4	1	..	0.5/1
7/29	3	3.0	0.8	12/10	10.5	9,300	..	..	..	38	..	49	..	3	10	..	1/1
8/ 6	..	...	...	....	12	8,900	..	..	3	38	..	47	..	6	6	..	...
Patient No. 2 (A. O. D.)																	
4/30	Admission	...	...	....	10	11,800	..	..	6	47	7	35	..	4	1	..	...
5/13	7	0.8	0.5	18/9.5	10	14,400	..	..	12	54	..	30	..	3	1	..	6/2
5/20	11	0.5	0.7	23/15	9	18,300	..	..	2	50	3	38	3	4	..	..	5/2
5/27	7	1.1	1.1	....	....	.....	..	..	..	..	..	..	..	..	..	..	2/1
6/ 3	11	0.7	0.1	27/—	8.0	13,600	..	..	1	48	..	43	..	6	2	..	3/2
6/10	9.5	0.3	0.9	....	9.5	11,500	..	..	5	49	2	40	..	3	1	..	3/2
6/17	7	...	0.6	....	8.5	9,400	..	..	3	47	..	36	..	6	8	..	4/2
6/24	8	0.7	1.2	18/10	10.0	5,500	..	..	..	24	5	59	..	10	1	1	5/3
7/ 1	9	0.5	0.6	....	10.5	8,800	..	..	1	35	2	48	..	11	3	..	7/3
7/ 8	8	0.5	0.5	10/—	11.5	9,600	..	..	8	45	..	44	..	..	3	..	3/2
7/15	8	0.4	1.0	6/6	10.5	5,600	..	..	10	42	..	45	..	..	3	..	2/1
7/22	6	0.6	0.6	12/8	10.5	5,300	..	..	4	30	..	55	..	5	6	..	3/2
7/29	10	0.2	1.1	....	11.0	8,800	..	..	..	42	..	48	..	7	3	..	2/1
8/ 6	..	...	...	....	12.5	6,300	..	..	3	41	..	49	..	3	1	..	...
Patient No. 3 (R. E. P.)																	
6/18	Admission	...	...	....	11.5	10,800	..	..	7	77	..	11	..	5	..	..	...
6/24	11	0.8	0.2	....	11.0	7,000	..	..	2	65	..	25	..	8	..	..	3/1
7/ 2	11	1.0	0.6	....	12.5	8,400	..	..	4	67	1	23	..	5	..	..	2/1
7/ 8	11	0.4	0.1	....	17.0	5,300	1	..	8	59	..	30	..	0	2	..	2/1
7/15	3	1.2	1.0	....	12.5	8,800	..	..	3	49	..	46	..	2	..	..	5/3
7/22	11	0.4	0.6	....	11.5	5,800	..	..	11	47	..	36	..	4	2	..	5/3
7/29	11	0.1	0.9	....	11.5	7,600	..	..	10	41	..	41	..	8	..	..	4/3
8/ 6	..	...	...	....	13.0	6,400	..	..	..	51	..	39	..	4	6	..	...
Control (N. B.) (miliary tuberculosis only)																	
5/ 3	Admission	...	...	....	10	15,200	..	..	1	43	6	45	3	0	0	1	...
5/16	2	3.4	1.8	19/19	12.5	13,900	..	..	18	21	..	52	..	9	..	..	...
5/23	2	1.4	1.2	....	11	7,900	..	..	10	24	1	59	..	1	5	..	2/1
5/31	2	0.0	0.4	....	....	.....	..	..	..	..	..	..	..	..	..	..	2/1
6/ 6	6	0.8	1.5	....	8.5	5,200	..	..	1	30	6	53	..	5	4	1	2/1
6/13	5/1	0.5	0.5	....	9.5	.....	..	..	..	..	..	..	..	..	..	..	...
6/20	2	1.7	2.2	....	9.0¶	8,800	..	..	..	46	..	43	..	8	3	..	2/1
6/27	2	0.5	0.6	7/6	10.5	5,600	..	..	5	35	..	60	..	7	3	..	2/1
7/ 4	2.5	0.1	0.7	....	10.5	8,000	..	..	1	34‖	..	47	..	7	4	7	1/1
7/11	2	...	1.0	14/14	10.5	9,300	..	..	6	46	..	43	..	1	3	1	1/1
7/18	1.5	1.0	0.2	12/12	10.5	8,300	..	..	..	24	..	70	..	7	2	..	1/0.5
7/25	2	0.7	0.1	16/16	10.5	9,300	..	..	7	29	..	50	..	10	2	..	1/0.5
8/ 1	1	0.6	0.1	18/18	11.5	6,600	..	..	2	39	..	53	..	4	2	..	1/0.5

* Cerebrospinal fluid.

† Acute otitis media with parenteral diarrhea, dehydration, and acidosis.

‡ 14 degenerated cells.

§ Transfused with 150 cc. whole blood.

‖ 7 degenerated cells.

¶ Transfused with 100 cc. whole blood.

The first three patients, and a fourth, with miliary tuberculosis alone, who served as a control, were subjected to detailed determination of serum and cerebrospinal fluid isoniazid levels and additional laboratory studies. The data on these studies are shown in Table 7. Serum levels showed an average peak three to four hours after doses, and cerebrospinal fluid levels an average peak in four to six hours, with higher levels in the serum than in the cerebrospinal fluid. There was more variation in the serum than in the cerebrospinal fluid levels. The patient with only miliary tuberculosis had no appreciable difference in levels.

METHOD OF ISONIAZID LEVEL DETERMINATION

Serum and spinal-fluid isoniazid levels were determined by the method of S. H. Rubin and co-workers.[10] Samples were frozen in sterile vacuum tubes and studied all at one time. Certain modifications were introduced into the procedure which have given more reproducible results in our hands. These are as follows:

(*a*) Potassium permanganate solutions were prepared fresh every month.

(*b*) Ammonium buffer was prepared fresh every two weeks.

(*c*) A standard solution of isonicotinic acid was assayed with each series of unknowns.

(*d*) Phosphate buffer was used to dilute the standards as well as the unknowns before the addition of cyanogen bromide.

(*e*) Readings were begun immediately after the addition of the cyanogen, since the rate of color development varied with each specimen.

Preformed isonicotinic acid was determined in each sample. The calculation is as follows:

$$\gamma/\text{ml.} = \frac{A - 1.5\,(B)}{S} \times \frac{5}{0.75} \times F$$

A = Optical density reading of unknown on Coleman Jr. spectrophotometer at wave length of 430 mμ

B = Optical density reading of blank (preformed isonicotinic acid)

S = Optical density reading of standard

$F = \frac{1}{0.898}$ = factor for converting milligrams per 100 cc. of isonicotinic acid to milligrams per 100 cc. of isoniazid

Duplicate determinations on unknowns, on standards, and in recovery experiments showed reproducibility of ±5%.

Recovery experiments indicated the ability of the procedure, with the described modifications, to account for concentrations within ±10% of the theoretical value.

For isoniazid determinations in spinal fluid, no protein-free filtrate was prepared. Thus the above calculations must be modified to account for the change in dilution.

COMMENT

Although it was a new experience to influence the course of tuberculous meningitis with any form of therapy, the results obtained in the first series were not satisfactory. The mortality rate was high, and the frequency of complications was distressing. Life expectancy was relatively short for most of the children in whom the disease was apparently arrested but who were suffering from serious nervous-system damage.

Administration of streptomycin intrathecally often is a difficult therapeutic problem. Cooke and co-workers [11] in the initial report on the use of intrathecal streptomycin for this disease, commented on the high fever and increased cerebrospinal fluid cell count after such injections. Levinson [12] was an early advocate of treatment without intrathecal streptomycin. McKay and co-workers [13] have reported 14 serious reactions to intrathecal streptomycin with three probable and two pos-

sible fatalities among 90 patients treated for meningitis with repeated injections; 6 of the 14 had tuberculous meningitis. O'Dell, Mardis, and Tempel [14] obtained better results in adults without intrathecal treatment than with it. In our earlier series, this form of therapy frequently had to be interrupted because of serious reactions.

In the current series, once treatment was well established, we were impressed by the scarcity of symptoms and signs of serious illness in those children who recovered. There were no complications, and the results were good.

The combination of the three drugs in the present regimen is logical. The value of paraaminosalicylic acid in delaying the emergence of streptomycin-resistant tubercle bacilli is well established. Recently, the Committee on Therapy of the American Trudeau Society [9] has called attention to the fact that isoniazid-resistant tubercle bacilli appeared rapidly when the drug was used alone and that the emergence of resistant strains may be prevented or delayed by the simultaneous use of streptomycin or paraaminosalicylic acid or both. The Committee recommended that if isoniazid is used, streptomycin or paraaminosalicylic acid or both should also be given.

Isoniazid levels ranged from 0.1 to 4.6 γ per milliliter in the serum and from 0.1 to 2.2 γ per milliliter in the cerebrospinal fluid, regardless of the time, up to 11 hours after the last dose of the drug. These levels are greater than the concentration of 0.06 γ per milliliter which has been reported to inhibit completely the H37Rv strain of Mycobacterium tuberculosis in vitro.[15] Also, there was no evidence of toxicity and the serum levels were well below the plasma drug concentrations which have been reported to be toxic for animals.[8]

The early recognition of cerebrospinal-fluid block is important, as it may be a cause of therapeutic failure. In our earlier series, hydrocephalus was present in two of the surviving and in at least five of the deceased patients and was found in four of the five on whom autopsy was performed. In addition, it occurred in one of the deceased patients of the newer series. The general aspects of the problem of block recently have been reviewed by Lincoln and Sifontes.[7] Smith and Vollum [16] have used diluted tuberculin (PPD) intrathecally in an effort to treat block, and they, as well as others,§ have advocated various neurosurgical approaches designed to allow administration of streptomycin above the point of obstruction. We have had no experience with the use of tuberculin and neurosurgical procedures, and our one trial of enzymes was inconclusive. When indicated, early modification of our treatment to include these procedures may have to be considered. Also, whether the present regimen of treatment without injection of streptomycin into the cerebrospinal fluid will be satisfactory depends on further evaluation. Nevertheless, it is our belief that any schedule which includes intrathecal injections of irritating materials cannot be considered as an ideal form of therapy for this disease.

The importance of early diagnosis and adequate treatment should be emphasized. The pathology of tuberculous meningitis indicates that successful therapy is primarily dependent on early detection of the disease, before irreversible damage has occurred.

§ References 17, 18, and 19.

SUMMARY

Data are presented on the results of the treatment of two series of patients with tuberculous meningitis, the first treated by the conventional schedule of intramuscular and intrathecal streptomycin with oral paraaminosalicylic acid and/or thiazolsulfone (Promizole) and the second treated with intramuscular streptomycin and oral paraaminosalicylic and isoniazid, without intrathecal streptomycin.

Serum and cerebrospinal-fluid isoniazid levels for the first three patients of the second series are included.

Results warrant further clinical trial of the new regimen.

Dr. Morris A. Lambdin, Salisbury, Md., helped to organize the studies of the second series while Resident in Pediatrics; Dr. Frank Stafford, Director, and Miss Sarah Ward, Chief Technician, Blue Ridge Sanatorium, Charlottesville, Va., assisted in making acid-fast cultures of spinal fluid; Sol Green,, Ph.D., gave advice in standardizing isoniazid determinations, Mr. Pierre Scott and Mrs. Jesse Cumbia gave technical assistance, and Miss Susan Taylor aided in preparing the tables and did the typing.

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CHEMICAL CONTROL OF RESPIRATION IN NEWBORN INFANTS

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IT IS THE purpose of this paper to analyze and define the nature of respiratory stimuli in the newborn infant as distinct from the mature adult, using data on blood gases and blood pH obtained in this laboratory on a series of newborn full-term infants.

The major stimulants to a normal respiration in adult humans and experimental animals have been studied extensively. The mechanisms by which they work are discussed in our modern textbooks of physiology, with emphasis on adult data. This report is concerned with an evaluation of the relative importance of the major stimulants to respiration in the blood of the newly born infant and includes a discussion as to the variable importance of these stimulants (hypoxia, blood pH, and plasma carbon-dioxide tension and content) and how these variabilities might shift the impetus for control of respiration in the newborn infant. An attempt is made to correlate the levels of these factors with those found in a man breathing normally and with pertinent experimental data.

MATERIAL AND PROCEDURE

Sixty-four full-term newborn infants were studied. Other data from 43 of these infants were reported previously.[1] A capillary blood sample was obtained from the heel of each infant at birth (within one hour of birth) and at some subsequent time during the first day of life, i. e., at either 4, 8, 12, or 24 hours of life. Blood specimens were placed on ice and taken to the laboratory for immediate analysis. No infant received oxygen, drugs, or chemotherapy during the observation.

All infants were full-term, ranging in weight from 2,400 to 4,450 gm.

As noted in Table 1, infants were delivered from mothers who received either nitrous oxide, drop ether, or caudal or saddleblock analgesia. No quantitation could be made as to the amount of nitrous oxide or ether administered to a given mother. The amount of cocaine derivative used in caudal and saddleblock analgesia is known, but this information has been omitted because no correlation with any of the chemical factors could be made.

TECHNIQUE AND METHODS

Capillary blood samples were drawn (under oil) from the heel for determination of blood pH, plasma CO_2 content, and oxygen content and oxygen capacity. The capillary blood sample was collected in an Exton blood plasma tube. The centrifuge tube had been coated with heparin in the following manner: The tube was filled with 4 cc. of 40 mg. per 100 cc. heparin solution and then placed in a vacuum oven at 65 C. and under diminished pressure of a water aspirator until dry.

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TABLE 1.—*Pertinent Clinical and Chemical Data Obtained on the Sixty-Four Infants Studied* *

Patient	Analgesia or Anesthesia	Length of Labor, Hr.	Birth Weight, Gm.	"Birth" Sample Drawn, Min. After Birth	pH		Carbon-Dioxide Content, mEq./L.		Carbon-Dioxide Tension, Mm. Hg		Oxygen Saturation, %		Oxygen Content, Vol. %	
					Birth	4 Hr.	Birth	4 Hr.	Birth	4 Hr.	Birth	4 Hr.	Birth	4 Hr.
Col	Section	..	3,290	28	7.32	7.38	21.3	20.4	39	34	82	93	18.1	21.2
Har	Saddle	8	3,870	20	7.32	7.37	23.6	22.0	43	38	79	90	18.2	23.8
Mue	Saddle	11	2,780	45	7.30	7.39	17.3	18.4	33	30	76	91	19.1	25.4
Bar	Saddle	16	3,210	34	7.30	7.39	22.6	22.5	43	37	88	89	22.2	23.6
Jad	Caudal	7	3,220	33	7.27	7.47	11.2	15.5	23	21	88	94	19.8	23.3
Hog	Saddle	10½	3,190	28	7.39	7.41	21.9	21.6	35	33	73	92	17.8	23.7
Woo	Caudal	2½	3,713	20	7.28	7.47	14.0	19.7	29	36	92	89	17.1	16.4
Orr	Caudal	3	3,515	60	7.35	7.41	19.8	19.3	34	30	95	94	25.5	23.9
O'Mo	Saddle	3½	3,205	34	7.36	7.39	18.8	18.6	33	30	91	93	23.1	23.2
Jun	Caudal	12	3,571	19	7.30	7.33	13.2	14.2	32	26	74	93	16.0	22.4
	Average.....				7.31	7.40	18.4	19.2	34	30	84	92	....	....
Hoa	N_2O-E.	32	4,450	35	7.33	7.44	15.2	13.4	27	19	75	91	20.2	26.9
Bar	Ether	3½	3,089	28	7.35	7.40	16.7	13.5	29	21	90	96	20.0	24.0
Boo	Ether	17	2,947	22	7.28	7.41	11.1	16.8	22	26	88	92	21.0	24.2
Fel	Ether	10½	3,684	16	7.32	7.39	17.1	18.9	32	31	74	93	19.8	24.2
Cul	Ether	4	3,401	10	7.38	7.42	17.9	18.5	29	27	89	89	16.7	18.0
Pab	Ether	21	3,401	25	7.35	7.43	20.0	21.5	34	31	83	88	20.0	23.7
Ruz	Ether	30	3,004	38	7.31	7.35	19.7	21.6	37	35	79	82	16.4	18.3
Bre	N_2O	5½	2,721	57	7.35	7.37	23.7	22.6	41	38	97	90	22.2	22.6
Pat	N_2O	12½	2,408	25	7.36	7.42	23.4	21.7	40	32	76	86	15.6	19.1
Hal	Ether	7	3,798	47	7.37	7.42	26.0	25.2	43	38	82	92	19.4	21.0
	Average.....				7.34	7.41	19.1	19.4	33	30	83	90	19.1	22.2
					Birth	8 Hr.	Birth	8 Hr.	Birth	8 Hr.	Birth	8 Hr.	Birth	8 Hr.
Lam	Caudal	9	3,730	40	7.35	7.45	18.7	21.8	32	30	87	93	19.9	22.2
Ral	Caudal	12½	3,630	43	7.35	7.40	22.0	21.8	38	34	94	93	20.0	18.5
Kob	Saddle	10	3,658	49	7.27	7.47	23.0	21.0	47	28	85	96	22.7	24.8
Fla	Saddle	3½	3,826	50	7.35	7.43	21.4	21.0	37	31	74	77	20.3	20.9
Whi	Caudal	3	2,550	45	7.33	7.43	19.5	20.9	35	30	83	90	16.6	17.6
Rob	.....	..	2,520	..	7.37	7.42	23.2	22.4	38	33	91	88	23.3	22.2
Bou	Caudal	6½	3,798	32	7.34	7.39	23.6	21.5	41	34	86	92	19.2	19.8
Pru	Caudal	12½	3,004	40	7.30	7.35	19.2	20.2	37	35	78	94	18.7	23.4
Den	Caudal	12½	3,798	40	7.38	7.44	18.9	18.8	31	27	80	95	18.6	22.0
Hol	Caudal	3	3,231	30	7.31	7.38	18.6	16.8	35	27	85	95	22.3	27.6
Ern	Saddle	4	3,205	36	7.35	7.35	22.4	22.4	39	39	76	90	18.3	23.3
	Average.....				7.34	7.41	21.0	20.8	37	32	83	91	....	....

					Birth	12 Hr.	Birth	12 Hr.	Birth	12 Hr.	Birth	12 Hr.	Birth	12 Hr.
Pat	Caudal	3½	3,310	35	7.37	7.42	20.0	20.1	33	30	86	96	23.0	25.9
Car	Caudal	4½	3,571	60	7.28	7.41	22.0	18.1	44	28	96	93	22.9	21.9
Nie	Caudal	9½	3,430	30	7.35	7.48	17.0	17.2	31	23	87	93	21.6	24.4
Bec	Saddle	2½	3,089	29	7.35	7.49	20.0	22.1	35	29	88	94	21.1	22.5
Swa	Caudal	24	2,781	30	7.34	7.50	16.2	19.4	28	24	88	94	21.5	24.9
Van	Saddle	4½	.....	36	7.33	7.45	23.1	21.1	41	30	73	86	16.2	20.5
Goo	Saddle	12	2,834	21	7.41	7.45	18.9	18.3	29	26	93	92	23.2	23.8
Wat	Caudal	7½	3,146	24	7.36	7.47	18.4	19.6	32	26	78	99	18.7	22.1
Whl	Saddle	3½	3,175	33	7.39	7.46	19.4	19.3	32	27	90	90	23.3	25.0
Wis	.....	2	3,270	17	7.29	7.38	21.6	17.8	42	29	82	89	22.0	24.0
	Average.....				7.34	7.45	19.6	19.3	33	27	86	92	....	....
					Birth	24 Hr.	Birth	24 Hr.	Birth	24 Hr.	Birth	24 Hr.	Birth	24 Hr.
Spa	Caudal	7	3,100	20	7.48	7.33	20.8	20.2	27	35	94	87	23.2	20.3
Fre	Caudal	9	3,720	65	7.37	7.49	22.4	24.9	37	32	84	93	20.4	18.1
Tao	Caudal	7	3,680	70	7.36	7.48	19.9	18.6	34	25	94	88	21.7	20.1
Joh	Caudal	5½	4,252	64	7.33	7.41	23.6	22.5	42	35	82	91	21.4	22.4
Sch	Caudal	3	3,004	34	7.42	7.50	21.2	23.2	31	28	83	96	20.0	22.9
Sea	Caudal	3½	3,741	55	7.29	7.36	20.9	19.5	41	33	84	84	20.7	18.9
Jub	Saddle	5	2,862	42	7.37	7.37	22.6	22.7	38	38	85	89	17.6	19.9
Law	Caudal	6	.....	31	7.42	7.48	18.3	16.1	28	22	90	88	19.5	20.6
Mil	Caudal	14	2,780	25	7.30	7.43	18.3	20.8	35	30	89	91	18.7	20.2
Dav	Saddle	8½	3,146	18	7.33	7.44	19.2	18.7	35	27	83	92	18.5	21.2
Wel	Saddle	11	3,542	21	7.34	7.40	19.1	21.2	34	33	76	100	19.9	26.3
Ros	Reade	10	3,260	25	7.37	7.41	24.5	19.2	40	30	83	95	21.0	25.2
	Average.....				7.36	7.43	20.9	20.6	35	30	85	91 (92 comp.)	....	....
Joh	N_2O-E	9	2,977	15	7.20	7.45	14.2	18.9	34	26	85	96	18.4	18.5
McL	Ether	8	3,373	15	7.27	7.46	17.9	19.8	37	27	77	90	17.8	20.7
Alb	N_2O	6	3,378	16	7.33	7.41	20.6	22.7	38	36	82	89	20.4	24.9
Bou	N_2O	14	3,836	45	7.29	7.42	21.3	22.4	42	33	85	89	19.1	17.7
Neu	Ether	2	3,515	47	7.40	7.40	24.3	23.3	37	36	89	91	18.2	17.9
Bry	Ether	4	3,458	25	7.35	7.48	20.8	21.1	36	28	78	85	17.9	19.3
Sim	N_2O	7	3,260	45	7.33	7.46	19.9	16.8	35	23	92	95	25.5	26.4
Bur	N_2O-E	11	3,373	60	7.36	7.45	13.4	17.5	23	24	82	91	22.5	23.2
Ric	Ether	4	2,891	60	7.35	7.42	20.1	19.2	36	29	92	90	24.0	23.9
Gil	N_2O	12	2,692	20	7.31	7.52	19.4	17.1	37	21	90	97	20.9	21.5
Ber	Ether	10	3,713	47	7.28	7.51	20.6	18.9	41	23	85	91	18.8	21.1
	Average.....				7.32	7.45	19.2	19.8	36	28	85	92	20.3	21.4

* No infant received any drugs, chemotherapy, or antibiotics during the study. No mother had been sedated at a time when any effect on the infant might be expected.

TABLE 2.—*Blood Gas and pH Determinations in Newborn Infants During the First Day*

Type Analgesia or Anesthesia	No. Infants	pH			CO_2 Content, mEq./L.			CO_2 Tension, Mm. Hg			% O_2 Saturation		
		Birth	Hr. After Birth		Birth	Hr. After Birth		Birth	Hr. After Birth		Birth	Hr. After Birth	
Inhalation	11	7.34	4	7.41	19.1	4	19.4	33	4	30	83	4	90
Caudal or saddle	10	7.31	4	7.40	18.4	4	19.2	34	4	30	84	4	92
Caudal or saddle	11	7.34	8	7.41	21.0	8	20.8	37	8	32	83	8	91
Caudal or saddle	10	7.34	12	7.45	19.6	12	19.3	33	12	27	86	12	96
Caudal or saddle	12	7.36	24	7.43	20.9	24	20.6	35	24	30	85	24	91
Inhalation	10	7.32	24	7.45	19.2	24	19.8	36	24	28	85	24	92
Total	64												
Average (Total group)		7.33		7.43	19.7		19.9	35		30	85		91
Range		7.20-0.48		7.33-52	11.1-26.0		13.4-25.2	22-47		19-39	73-97		77-100
Spread		0.28		0.19	14.9		11.8	25		20	24		23

Samples were kept at 0 C. until the analyses were performed. That portion to be used for the pH determination was sucked into a tuberculin syringe (1 cc.) through a 5.0-cm. hypodermic needle. The air in the syringe was replaced by a small amount of mineral oil covering the sample.

Blood pH was determined with use of the Cambridge Electron Ray pH meter (research model). The meter was kept in an incubator which was maintained at a temperature of 38C. All determinations were performed at this temperature. The blood sample was injected from the tuberculin syringe, after the needle was removed, into the microcondenser type glass electrode through the top end of the electrode. Ten minutes was allowed for temperature equilibration before readings were taken. The meter was calibrated before each sample and checked again afterward with pH standards solution prepared from Coleman Buffer Tablets (7.40 pH + 0.02 at 30 C.

The oxygen content of the capillary blood was determined according to the method of Van Slyke.[2] A blood sample of 0.2 ml. was employed. For the measurement of oxygen capacity of blood the sample was rotated with 10 times its volume of air in a syringe for at least 20

TABLE 3.—*Relationships of Analgesia or Anesthesia Used to CO_2 Tension, Blood pH, and Blood Oxygen Saturation of Normal Full-Term Newborn Infants*

Type Analgesia or Anesthesia	No.	Birth		4-24 Hr.	
		Average	Range	Average	Range
CO_2 Tension, Mm. Hg					
Caudal	25	36	44-23	29	37-21
Saddle	14	36	47-29	31	39-26
Nitrous oxide	9	35	42-23	28	38-19
Ether	12	34	43-22	29	38-21
Blood Oxygen Saturation, %					
Caudal	30	87	74-96	92	84-99
Saddle	15	82	73-93	89	77-100
Nitrous oxide	9	85	75-97	92	86-97
Ether	12	85	74-92	90	82-96
Blood pH					
Caudal	30	7.33	7.20-0.48	7.42	7.33-0.50
Saddle	15	7.35	7.27-0.41	7.41	7.37-0.49
Nitrous oxide	9	7.32	7.20-0.36	7.43	7.35-0.51
Ether	12	7.33	7.27-0.40	7.42	7.37-0.51

minutes. Then the oxygen content was determined in the same manner as that before the sample was aerated. Oxygen saturation was calculated by the following formula:

$$\% \text{ oxygen saturation} = \frac{\text{vol. \% oxygen content}}{\text{vol. \% oxygen capacity}} \times 100$$

The CO_2 tension of the plasma (p CO_2 was calculated by the Lyon chart for graphic calculation of serum or plasma values by the CO_2 solubility equation and the Henderson-Hasselbalch equation.

RESULTS

Table 1 lists the infants and the data obtained at birth and when sampled subsequently during the first 24 hours of life. The average results obtained in the various subgroups are summarized in Table 2.

The average infant in this series is shown to have a rise in pH of 0.10, from an "acid" pH of 7.33 at birth, to 7.43. There was essentially no change in the total plasma carbon dioxide content (19.7 to 19.9) during the first day of life. There was, however, a decisive drop in CO_2 tension of 5 mm. Hg during this time, as well as a significant rise in blood oxygen saturation from 85% at birth to 91% in the few hours succeeding birth.

Correlations which were tried but with no success are the following: birth weight of infant *vs.* "birth" pH; age of mother *vs.* "birth" pH; age of infant in minutes *vs.* "birth" pH; age of infant in minutes *vs.* oxygen saturation; age of infant in minutes *vs.* "birth" CO_2 tension age of infant in minutes *vs.* "birth" CO_2 content.

As a matter of interest, the results were tabulated differently (Table 3) according to the type of analgesia or anesthesia given the mother, with no significant difference in findings noted at birth.

COMMENT

In order to clarify our attempts to evaluate the major stimuli affecting respiration in the newborn infant, a brief review of some of the physiology involved is necessary.

The major stimulants to normal ordinary respiration in adult humans are now generally believed to act through the "respiratory center," those poorly defined groups of nerve cells in the pons and upper medulla. It has been assumed that the activity of these centers can be adjusted to the metabolic needs of the body by means of a change in one or all three of the main components in the blood that are characteristic of metabolic activity, that is, oxygen tension, carbon dioxide tension, and hydrogen-ion concentration.

Ever since the discovery that oxygen is important to the maintenance of metabolism, physiologists have known that oxygen consumption parallels respiratory activity. It was then concluded that the need for oxygen provided a direct stimulus to the respiratory center.[3]

Later, however,[4] the respiration of man was shown to be too insensitive and variable in its response to oxygen lack to permit the belief that oxygen is the most important factor in control of respiration. Haldane and his collaborators[5] showed that carbon dioxide was a more potent and consistent stimulant to the respiratory center proper. It then became the general belief that both carbon dioxide and the hydrogen-ion concentration (by virtue of hydrogen ions dissociated from carbonic acid formed when CO_2 is dissolved in water) resulting from the CO_2 level were the major regulating factors. The hydrogen ion then came to be considered as the common denominator in the chemical control of respiration. Discrepancies persisted, however, but these were explained by Gesell * by making the assumption that the hydrogen-ion concentration within the respiratory center determines its activity, and thus the arterial blood would not always be in equilibrium with the respiratory center. So Winterstein[8] explained the hyperpnea of anoxemia as being due to the accumulation of acid products of incomplete oxidation within the cells of the respiratory center. Later experiments in Krogh's[9] laboratory led to the conclusion that carbon dioxide does not act solely by virtue of its acid-forming products but does have some specific effect in control of breathing.

This, then, leads back to Haldane's view that carbon dioxide, per se, is a specific regulator of respiration. It must be remembered that the response of the respiratory center to a given amount of stimulus is variable and, secondly, that changes in the hydrogen-ion concentration of the arterial blood are capable of setting up effective respiratory reflexes in the carotid and aortic bodies in other than normal control of respiration.

* References 6 and 7.

One would normally expect to find the stimulus to respiration in the newborn infant to be similar to that of adults and to arrive from one or all of these three primary stimuli. Our data have been analyzed to see, in fact, whether the situation in the newborn infant is similar to that of adults.

Carbon Dioxide Tension.—Figure 1 graphically represents the data presented in Tables 1 and 2 regarding levels of carbon-dioxide tension in the blood of the

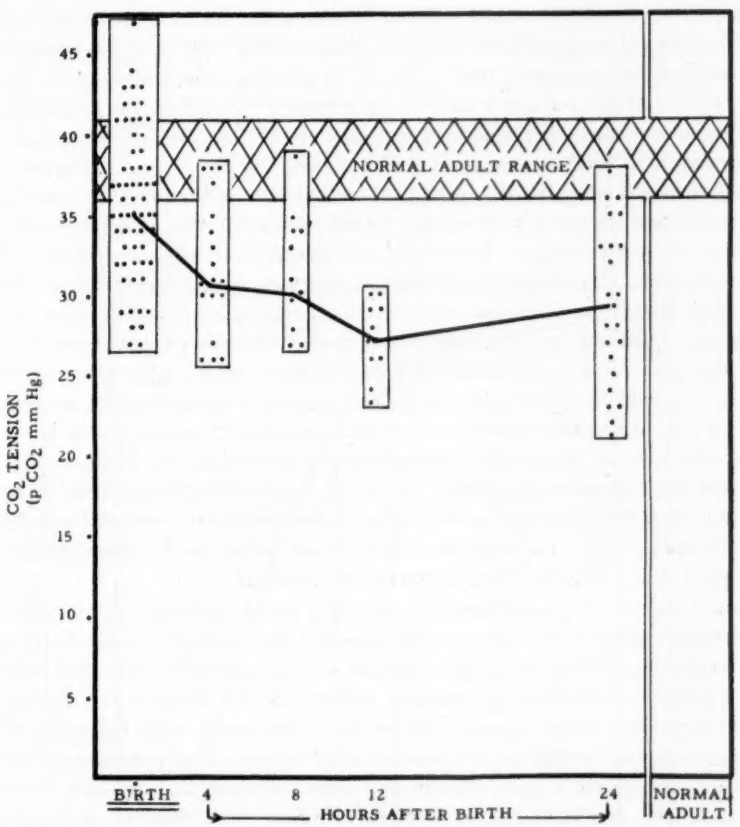

Fig. 1.—The relationship of the plasma carbondioxide tension of the newborn infant to the normal adult range. Each dot represents determination on one infant. The heavy black line represents the average. At birth many infants are within the "normal" adult range but subsequently at 4, 8, 12, and 24 hours of age are well below this level. See text for discussion.

normal newborn infant. Here it can be seen that the carbon-dioxide tension at birth is below the level of stimulation in a normal adult. Furthermore, this level significantly falls during the first day of life, indicating the CO_2 tension is being driven to a lower level by the impetus of some factor other than itself.

Carbon-dioxide tension when acting alone tends to inhibit respiration when it falls below the region of 40 mm. Hg, as well as to cause hyperpnea when the tension is above this level.

Infants are born in a state of acidosis,[1] due, not to an accumulation of carbon dioxide (with increased carbon-dioxide tension), but to an accumulation of some other metabolic product. In other words, the acidosis is a metabolic acidosis and not a respiratory acidosis due to a primary CO_2 retention. It would seem, then, that carbon-dioxide tension is not the driving force (either through CO_2 tension or blood pH) in establishing or maintaining respiration in the newborn infant in the first day of life.

Blood pH.—It is still a confused point as to what effect the blood pH itself has in regulating respiration during the first few hours of life both as to its strength as a stimulus and where it acts, that is, on the respiratory center itself or on the chemoreceptors (carotid and aortic bodies). It is known that in man (as in diabetic acidosis) there is often enough hyperpnea to reduce the alveolar and arterial carbon-dioxide tension to as little as one-half or less of normal (40 mm. Hg), or otherwise the hyperpnea would cease as soon as the CO_2 tension had been returned to normal. The newborn infant adjusts to a normal pH (adult standards) with an actual lowering of the CO_2 tension beyond an already subnormal level without evidence of extreme ventilation. Unpublished data from this laboratory reveal that this may well correlate with initially high plasma levels of other organic acids (lactic acid and pyruvic acid), which fall and level off concomitantly with the establishment of a normal blood pH. We are not certain that these organic acids, either alone or in addition to other stimuli, help regulate or govern pulmonary homeostasis in the first few hours of life. It has been shown clearly that the respiratory center of man is not nearly as sensitive to changes in hydrogen-ion concentration as Haldane first implied, and the hyperpnea of acidosis (in so far as it cannot be ascribed to an increase in carbon dioxide in the center) may be due entirely to reflexes from the carotid and aortic bodies, for these have been found to be readily stimulated by changes in pH well within the limits encountered clinically.[10]

Oxygen Tension.—In consideration of the third major stimulus to respiration, decreased oxygen tension, it is immediately apparent that newborn infants have at birth an oxygen-saturation and oxygen-tension level considerably less than that considered normal. One cannot immediately assume that this hypoxia is a driving force to respiration in these infants without first considering what the effect of hypoxia is on alveolor ventilation of a normal adult subject. It is generally agreed that the effect of hypoxia is quite variable, that increased alveolor ventilation is not obtained until 18% (or less) oxygen is being breathed, the hyperpnea of oxygen lack being typically much less intense than that of CO_2 excess.

It is the ordinary conception that oxygen lack causes a hyperpnea resulting from chemoreceptor reflexes (carotid and aortic bodies) and not from a direct effect upon the medullary respiratory centers. It is further generally agreed that chemoreceptor reflexes aroused by anoxia are not a factor in maintaining respiratory activity under ordinary conditions in the adult. In other words, oxygen lack seems to have the characteristics of a pathological rather than a physiological type of control.

Since the hyperpnea of anoxemia is generally conceded to be a chemoreceptor response (carotid and aortic bodies) the sensitivity of the chemoreceptors is determined by simply finding the smallest degree of reduction in oxygen tension at which respiration is stimulated. As noted in Figure 2, this corresponds with a diminution

of arterial oxygen tension from 90 mm. Hg at 95% saturation to 67 mm. Hg at 92% saturation. It is further understood that once this threshold has been passed, then further decreases in oxygen tension lead to hyperpnea of progressively increasing intensity, and this is the strongest chemoreceptor stimulant of any of the three chemical changes encountered in the blood under conditions compatible with life.

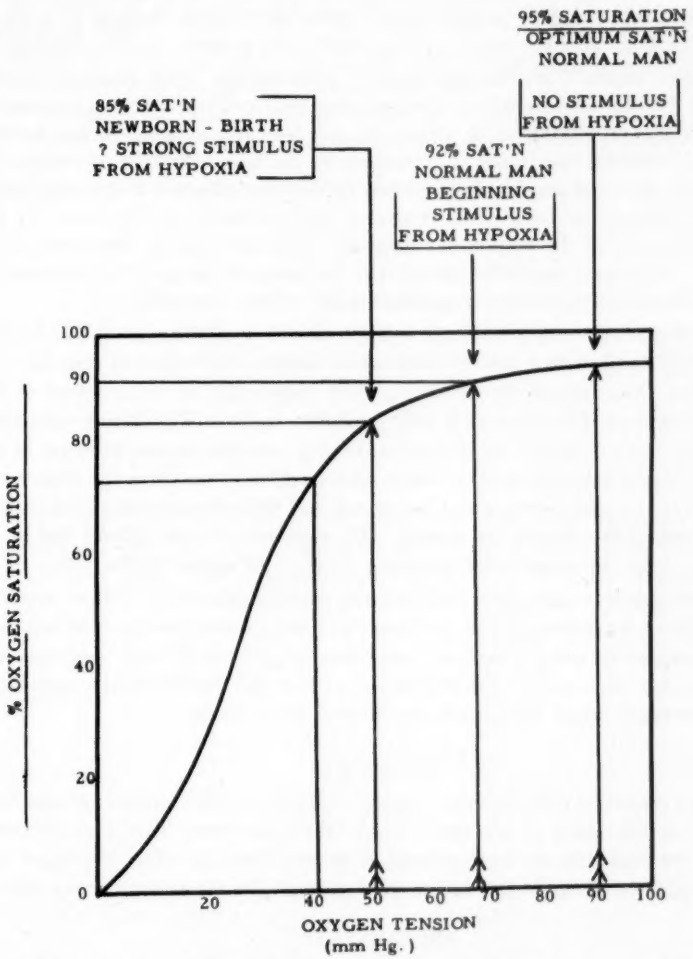

Fig. 2.—The oxygen dissociation curve of normal adult blood. The arrow at 90 mm. Hg (tension) points to 94 to 95% saturation, normal for arterial blood, normal adult. Other arrows point to other 0_2 saturation-tension relationships explained on the chart and in the text. The unmarked line at 0_2 tension of 42 mm. Hg (which meets the horizontal line at 74% saturation) represents the 0_2 saturation-tension relationship for the few infants with low blood oxygen saturation at birth.

Further reference to Figure 2 shows that the oxygen saturation and tension of infants at birth is considerably below the range of beginning effectiveness as a stimulant in adults. In other words, the oxygen tension of the blood of newborn

infants is well down in the range to elicit intense and effective hyperpnea if based on the same standards of observation made on normal adults. Thus, using the oxygen dissociation curve of adult type hemoglobin, one might well expect the oxygen tension in the blood of many newborn infants to be well below 55 to 60 mm. Hg at birth, which is extremely low by adult standards and effective in stimulating respiration. The oxygen dissociation curve for fetal type hemoglobin, which newborn infants possess to a degree, would further lower the oxygen tension at a given oxygen saturation. Further work on this point is in progress in this laboratory.

A previous report from this laboratory [11] substantiated other reports [12] of the phenomena that the administration of oxygen changes the Cheyne-Stokes respiration to an adult type of respiration in premature and full-term infants. It was further shown that breathing sometimes is stimulated by the administration of oxygen, as has also been demonstrated in adults. It has further been claimed that on this basis the normal pressure of oxygen in the arterial blood is below the optimum for the proper functioning of the respiratory neurons, which are slightly depressed at all times. It is, however, generally agreed that variations in oxygen tension tend to play a small part in respiratory regulation under normal conditions.[13]

The periodic breathing of newborn infants, as well as all Cheyne-Stokes breathing, has been ascribed to a teeter-board action between the effect of hypoxia and accumulating CO_2 through the following cycle: depression of the neurons of the respiratory center and diminution of their sensitivity to CO_2. Pulmonary ventilation is reduced as a result of this diminished sensitivity, and the oxygen pressure of the arterial blood falls below normal. Chemoreceptor reflexes then drive the respiratory center until the oxygen pressure rises to normal and the reflex stimulus is abolished. The hyperventilation lowers the arterial CO_2 pressure to such a level that it no longer stimulates the depressed respiratory center, and apnea results.

It is probable from data presented that the periodic breathing in these newborn infants is due to tissue oxygen lack and that this type of teeter-board action may well occur in respect to oxygen tension with alternating stimuli from hydrogen-ion increases rather than carbon dioxide per se, in that the carbon-dioxide tension is almost universally below the stimulatory level in these infants.

CONCLUSIONS

The data presented indicate there is great variability of the chemical stimulants to respiration in the blood of the newly born infant. It seems that a considerable portion of the total stimulus to respiration is derived from the effect of oxygen lack on the carotid and aortic bodies rather than through the respiratory center per se.

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HYDROCORTISONE OINTMENT IN THE TREATMENT OF INFANTILE ECZEMA

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REPORTS on the effectiveness of hydrocortisone ointments in the treatment of selected diseases of the skin have already been published.* Among the dermatoses treated with these preparations, atopic dermatitis responded very favorably in a large percentage of cases. This favorable response was also reported to occur in the infantile form of atopic dermatitis ("infantile eczema") in the few instances that the hydrocortisone ointments were used in patients 2 years of age or younger. These encouraging results, together with the advantages offered by a clean, odorless, nonstaining, nonstinging, apparently nontoxic ointment such as hydrocortisone ointment prompted us to extend the evaluation of this remedy to additional cases of infantile eczema.

The present study was undertaken as a joint project of the Dermatologic Service and the Pediatric Service of the University Hospital and was carried out in the special clinic for infantile eczema which had been in operation in the latter service for seven years. The established routine of this "Eczema Clinic," which includes, in addition to the dermatologic care, specific techniques in handling the allergic, nursing care, and psychosomatic problems,[4] was continued with the one exception of using hydrocortisone ointment topically instead of such previously used medications as 10-20-30 ointment (aluminum acetate [Burow's] solution, wool fat U. S. P., and zinc paste), iodochlorohydroxyquinoline (Vioform) cream and ointment, crude coal-tar ointments, etc.

In their place, a specially compounded ointment was used, consisting of wool fat U. S. P., 15%, liquid petrolatum, 10%, and white petrolatum, 75%. This vehicle without hydrocortisone served as the control in all of the studies and will henceforth, in this paper, be referred to as the "control ointment." To this control ointment, hydrocortisone free alcohol was added in a concentration of 25 mg. per gram to make a 2.5% hydrocortisone free alcohol ointment.†

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From the Department of Dermatology and Syphilology (Chairman, Dr. Marion B. Sulzberger) and the Department of Pediatrics (Chairman, Dr. Adolph G. DeSanctis), New York University Post-Graduate Medical School and the Skin and Cancer Unit and the Children's Clinic of the University Hospital, New York University-Bellevue Medical Center.

* References 1 to 3.

† The Medical Division of Merck & Company, Inc., Rahway, N. J., supplied the hydrocortisone free alcohol ointment and the control ointment.

Parents or others taking care of the babies were told to apply the hydrocortisone free alcohol ointment to the affected areas of the right side and the control ointment to the affected areas of the left side. Careful instructions were given concerning the application of the ointments and the amounts that should be used. Applications were made two or three times daily. Dressings were not recommended. All previous topical therapy was discontinued with the occasional exception of wet compresses of a dilute solution of aluminum acetate in a few cases. Daily cornstarch baths were permitted. Patients were seen at weekly intervals at the onset of treatment and at longer intervals thereafter.

TABLE 1.—*Effects of Hydrocortisone Free Alcohol Ointment Compared with Effects of Control Ointment On Symmetrical Sites*

Case	Age, Mo.	Duration of Dermatosis, Mo.	Duration of Treatment, Wk.	Degree of Improvement *	
				Control Ointment	Hydrocortisone Ointment
1	14	13	2	+	+++
2	20	18	1	0	++++
3	6	5	2	+	+++
4	7	6	5	++	++
5	19	17	1	+	++++
6	36	30	5	+	+++
7	10	6	2	+	+++
8	6	3	6	+	++++
9	48	42	2	0	0
10	7	5	1	++++	++++
11	6	6	5	+	+++
12	14	12	1	+	++++
13	13	11	7	0	0
14	4	3	1	+	++++
15	18	18	1	++	++
16	6	5	2	+	+++
17	12	8	5	+	++++
18	6	4	1	+	++++
19	28	24	4	0	++++
20	4	3	3	+	++
21	4	3	3	+	+
22	5	4	2	+	+
23	6 yr.	5½ yr.	2	0	0
24	42	42	2	0	+++
25	2	2	1	0	0
26	6	3	1	0	++++
27	10	8	1	0	0
28	15	15	3	+	+
29	5	4	3	++	++
30	12	10	1	+	++

* 0 indicates no change; + indicates up to 25% improvement; ++ indicates 25 to 75% improvement; +++ indicates 75 to 90% improvement, and ++++ indicates 90 to 100% improvement.

As a rule, both a dermatologist and a pediatrician examined each patient at each visit.

Selection of cases was random; all old cases were changed to the new topical approach, and all new cases were started on the present regimen at the time of their first visit. Exceptions were made in the case of patients almost well on previous therapy and patients with insufficient involvement. In a few additional instances, language difficulties led us to believe that proper parent cooperation would not be possible, and such cases were also excluded.

Almost all the infants treated presented the typical picture of the infantile form of atopic dermatitis, with involvement of the characteristic areas—the head (primarily the face), the trunk, and the extremities. In several instances, the

TABLE 2.—*Summary of Results of Treatment*

	Hydrocortisone Ointment		No. with Equal Improvement on Both Hydrocortisone Ointment- and Control Ointment-Treated Sides
No. Cases	No. With Improvement	No. Without Improvement	
30	18	5	7

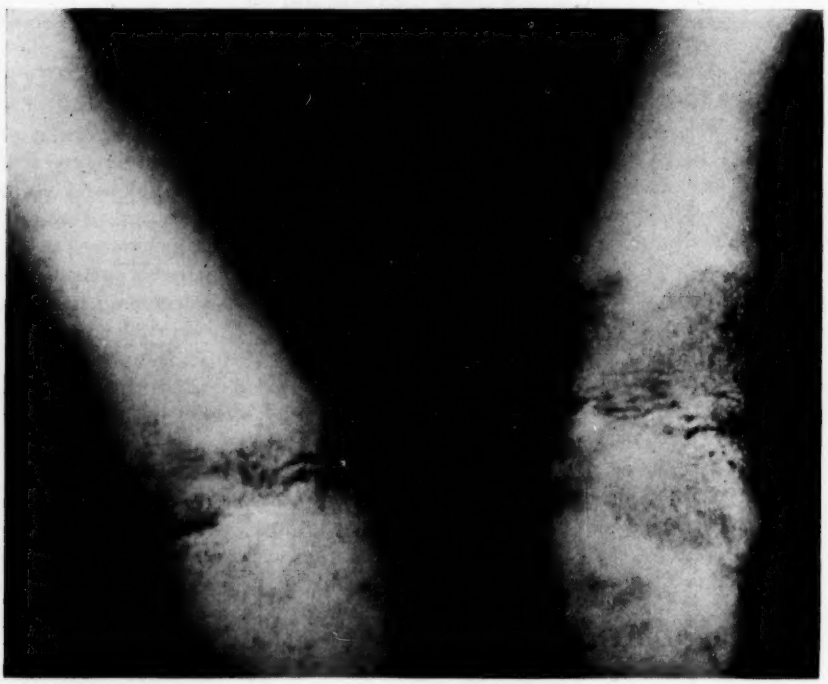

Fig. 1 (Case 5, D. W.).—The antecubital fossae are typical areas of involvement for atopic dermatitis. The right fossa was treated with hydrocortisone ointment and the left with the control ointment. The duration of application was one week.

involvement was generalized. The rather classic clinical picture of erythema, moderate edema, oozing, and crusting was common, as were the papular and papulovesicular forms. A few cases presented the drier form, with beginning thickening and lichenification of the involved skin.

Itching was the predominant symptom, as evidenced by the active scratching of the child or by the presence of excoriations.

Response to therapy was considered favorable when there was a lessening of erythema and edema, as well as diminishing oozing and crusting. Improvement

was also judged by the disappearance of excoriations and of other evidences of damage done by rubbing and scratching. Parents stated that itching subsided rapidly as judged by the diminished scratching and decrease in degree of restlessness of the very young infants. In addition, they were questioned concerning the side of the body they felt had done better and as to how soon improvement was noted.

RESULTS AND COMMENT

Table 1 summarizes the observations on 30 children treated by the "simultaneous paired comparison" method in which hydrocortisone free alcohol ointment was applied to the affected areas of the right side of the body and control ointment to

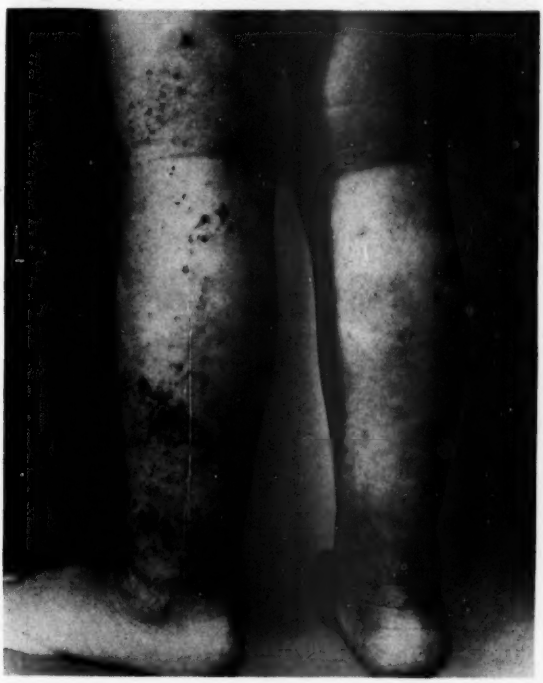

Fig. 2 (Case 6, P. S.).—Results of five weeks of continuous therapy. The hydrocortisone ointment was used on the right lower extremity and the control ointment on the left.

the contralaterally affected areas of the left side. Favorable response to the hydrocortisone free alcohol ointment was noted in 18 (67%) of these patients. Where benefit was achieved, it was obvious at the time of the first follow-up visit—one week after the beginning of treatment. In many instances, the mother stated that the improvement was visible within 24 to 48 hours after first application of the ointment.

While some degree of improvement was noted on both sides in 14 of these 18 patients, it was definitely greater on the side treated with hydrocortisone free alcohol ointment, as contrasted with the side treated with the control ointment (Tables 1 and 2, Figs. 1 to 4).

The control ointment-treated side did as well as the hydrocortisone ointment-treated side in seven instances (Table 2). The hydrocortisone ointment-treated side cleared almost completely, while the control ointment-treated side remained unchanged in three patients. In only five cases was there no (or questionable) improvement on either of the treated sides.

At the time of writing there was no case in which therapy had been discontinued for a sufficiently long time to find out to what degree a patient's condition would relapse. Once improvement was achieved, it could often be maintained on a reduced schedule of use of the hydrocortisone ointment.

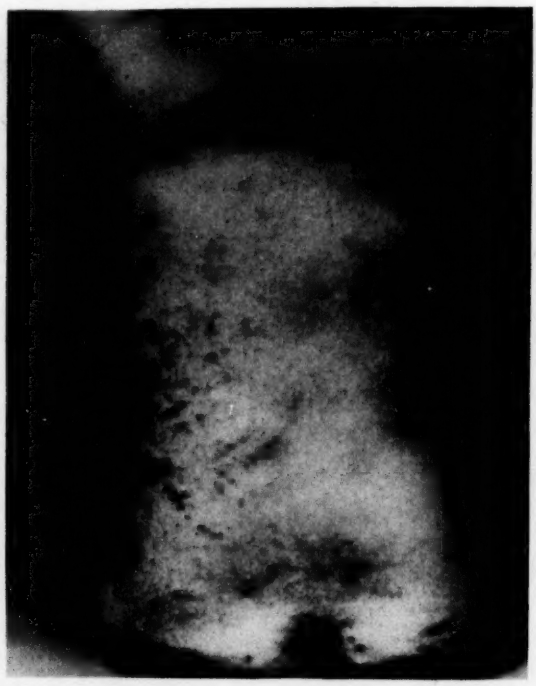

Fig. 3 (Case 7, J. F.).—Photograph taken after one week of use of hydrocortisone ointment on the right side and control ointment on the left. The mother stated that improvement was noted on the right side within 24 hours.

There were no instances in which an intolerance to the medications was noted. It was not necessary at any time to discontinue the ointment because of clinical evidence of irritation, allergic eczematous contact dermatitis, or for any such disagreeable reason as staining of skin or bed linens, odor, or stinging or burning sensations. In no instance was a spread of local superimposed infection noted as a result of the repeated and prolonged topical application of the hydrocortisone ointment. In nine infants (all under 14 months of age), approximately one-half or more of the body surface was inuncted with the hydrocortisone free alcohol ointment two to three times a day for one to seven weeks without a single instance of clinically

evident undesirable systemic effects due to absorption of the hydrocortisone. Of course, it should be fully realized that surveillance must be kept on every patient exposed to a new drug. In this regard, it is of importance to know that no absorption of hydrocortisone acetate from the ointment well inuncted into either normal or diseased skin could be demonstrated according to the method used by C. C. Smith.[5]

While there are several possible explanations to account for the improvement of involved areas distant from the sites of actual application of the hydrocortisone free alcohol ointment, the most likely is that the hydrocortisone ointment, though applied to only one side, is, nevertheless, spread to clothing, towels, bed clothing, etc., and

Fig. 4 (Case 12, D. M.).—The result of one week of treatment with hydrocortisone ointment on the right side and the control ointment on the left. The patient originally presented a generalized erythematous maculopapular eruption with considerable oozing and crusting.

in this way comes in contact with the untreated (control) side. This is particularly true of the face of the child who is constantly turning and twisting from side to side on the pillow or bed linen. It was on the face that the differences in therapeutic response were the most difficult to differentiate. The chance that there may be local skin absorption with resulting systemic effect must also be considered, although this possibility appears to us to be very remote.

SUMMARY AND INFERENCES

Thirty cases of infantile eczema were treated by the "simultaneous paired comparison" method with 2.5% hydrocortisone free alcohol ointment on one side and the vehicle alone on the other side. Favorable response to the hydrocortisone oint-

ment was noted in 18 of these patients. We are of the opinion that in the general run of cases the hydrocortisone ointment as used in these studies constitutes the simplest, cleanest, and most rapidly effective of all the topical measures we have employed in the treatment of infantile eczema.

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PHYSIOLOGIC HYPERBILIRUBINEMIA IN PREMATURE INFANTS

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THE PRESENT paper represents an attempt to investigate, with more precise quantitative data than have been available previously, the well-established clinical impression that physiologic jaundice occurring neonatally in prematures is of greater intensity and longer duration than that observed in infants born at term.* Clinical icterus is stated also to occur more frequently in prematures.† Physiologic jaundice of the newborn is now generally attributed to hepatic failure to excrete bilirubin completely.‡ The assumption that prematures demonstrate greater deficiencies in hepatic excretory ability than normal newborns is consistent with observations of other functional differences between these two groups.[9] Such an assumption is also inherent in the concept that the "degree of hyperbilirubinemia is a measure of the functional maturity of the infant at the time of birth" [10] and with the statement appearing in an older text that "in general, body weight and the intensity of the icterus are inversely proportional." [11] However, since plasma bilirubin is a more accurate index of the severity of the phenomenon than subjective interpretations of degrees of jaundice and since the latter may be dependent upon local tissue factors entirely unrelated to the mechanism responsible for the hyperbilirubinemia,[12] a quantitative study of plasma bilirubin levels in prematures was undertaken.

There are few reports of icterus neonatorum in prematures.§ Ylppö,[13] from his extensive investigations, concluded that physiologic jaundice was more intense and of longer duration in premature than in term infants. However, several of the premature infants were anemic, and the possibility that jaundice was aggravated by hemolysis or sepsis cannot be excluded. Taylor [14] demonstrated that the icterus index remained elevated for prolonged periods in prematures. Hirsch [15] found that the highest cord-blood bilirubin concentrations occurred in prematures.

Read by title at the meeting of the Society for Pediatric Research, Old Point Comfort, Va., May 5, 6, and 7, 1952.

From the Departments of Pediatrics, Louisiana State University School of Medicine and the Tulane University of Louisiana School of Medicine, and Charity Hospital of Louisiana.

* References 1 to 4.

† References 5 and 6.

‡ References 7 and 8.

§ References 13 to 21.

Bonar [17] and Larsen and With [18] noted the variability of physiologic hyperbilirubinemia and were unable to demonstrate any correlation between degrees of prematurity and extent of bilirubinemia. Schick, Weiner, and Reiner [19] were unable to correlate birth weights with cord-blood icterus indices and found that statistical comparisons among normal, premature, and postmature infants were of doubtful significance.

Findlay, Higgins, and Stanier, [20] similarly, could show no association between cord-blood bilirubin and fetal maturity, although their studies reveal a higher incidence of clinical jaundice in premature infants. Illustrative serial bilirubin curves

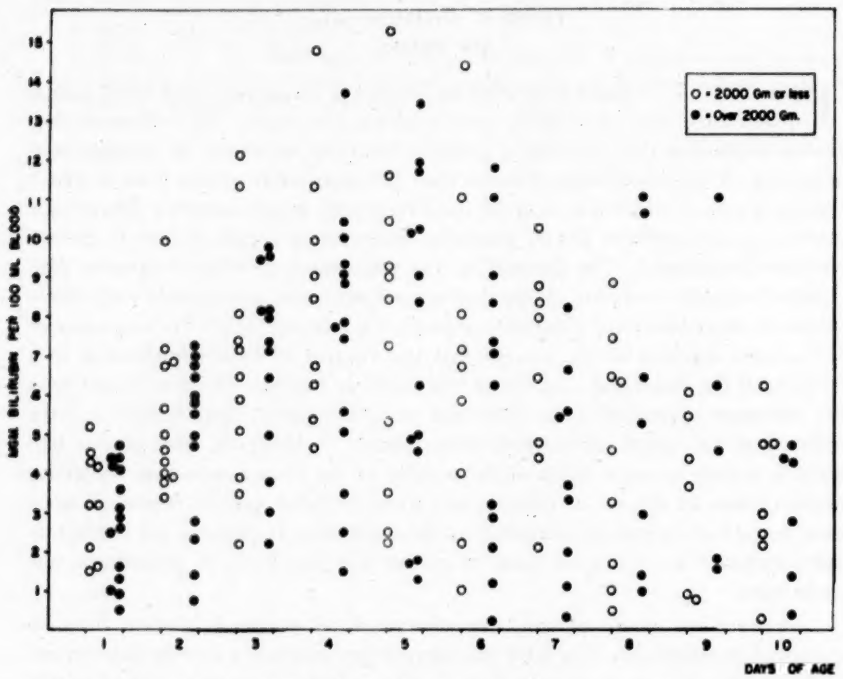

Chart 1.—Distribution of plasma bilirubin values, in milligrams per 100 ml., in 27 premature infants for the first 10 days of life.

for the four prematures in their study show distinctly higher levels than were demonstrated for normal infants. More recently, Hsia and co-workers [21] observed higher serum bilirubin levels in prematures and concluded that physiologic jaundice is severer and of longer duration than in term infants.

MATERIAL AND METHOD

Twenty-seven premature and 12 term infants constitute the subjects of this report. Of the prematures, 21 were Negro and 6 were white infants. Eight term infants were Negro, and four were white. Because parturient mothers remain in the hospital only one to three days, parallel studies on a larger number of normal infants were not carried out. The full-term infants were delivered by Caesarean section.

Determinations of total plasma bilirubin were performed on heparinized venous blood according to the method of Malloy and Evelyn [22] as modified by Ducci and Watson.[23] Where possible, 0.5 ml. of plasma was used. In some instances, 0.2 ml. was used. Tests were carried out daily until the peak of the curve was reached and the downward slope clearly established. Additional values were then determined at intervals until the level attained was at or below 1.0 mg. per 100 ml., a figure regarded as the upper limit of normal for adults.[21] Ten of the 12 term infants did not remain in the hospital long enough to reach this level, discharge being effected between 7 and 10 days. In one of these the curve was still rising on discharge at seven days. Of the remaining two infants, one never exhibited any hyperbilirubinemia, while the other had a concentration of 0.8 mg. per 100 ml. by the fourth day. Of the prematures, four left the hospital before their bilirubin levels had returned to 1.0 mg. per 100 ml.

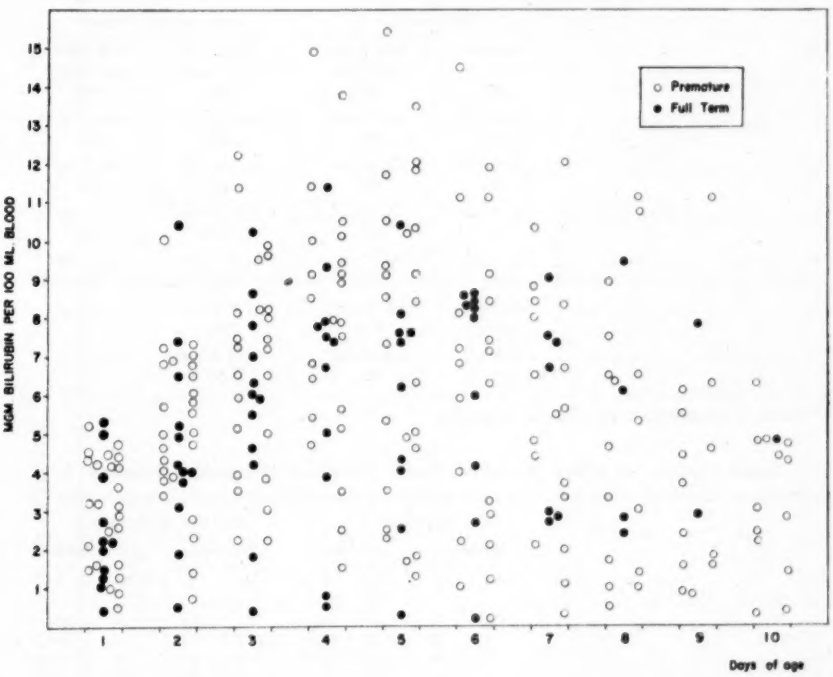

Chart 2.—Distribution of plasma bilirubin values in milligrams per 100 ml., for 27 premature and 12 term infants for the first 10 days of life.

RESULTS

Birth weights among the 27 prematures were less than 2,000 gm. for 11, were 2,000 gm. and over for 16, and ranged between 1,465 and 2,250 gm. Only one premature infant, weighing 2,010 gm. remained without jaundice, plasma bilirubin being consistently below 1.0 mg. per 100 ml. In two others, jaundice was minimal and transient, with maximum plasma bilirubin concentrations reaching 3.0 and 2.3 mg. per 100 ml. The remaining 24 prematures were all moderately to markedly icteric. Of the term infants, only two were free from jaundice. In one of these,

plasma bilirubin never exceeded 0.5 mg. per 100 ml. In the other, the maximum concentration of 1.9 mg. was reached on the second day, and a normal level was achieved on the fourth day.

The plasma bilirubin values for all prematures during the first 10 days of life are shown in Chart 1. The subjects are divided into two weight groups, those below and those above 2,000 gm. Within each of the two groups there is a wide but similar range.

TABLE 1.—*Daily Mean Plasma Bilirubin Values, in Milligrams per 100 Ml., and Standard Deviation in Premature and Term Infants* of this Series and that of Hsia and Co-Workers* [21]

	This Study		Hsia and Co-Workers	
Day	Premature	Full Term	Premature	Full Term
1	2.98 ± 1.40 (24)	2.68 ± 1.66 (11)	5.41 ± 3.16 (13)	5.66 ± 1.85 (21)
2	5.02 ± 2.08 (26)	4.80 ± 2.60 (12)	8.07 ± 4.40 (15)	6.80 ± 2.87 (24)
3	6.84 ± 2.73 (22)	5.85 ± 2.80 (10)	10.75 ± 6.44 (15)	6.21 ± 3.63 (24)
4	7.95 ± 3.37 (25)	6.04 ± 3.63 (12)	11.96 ± 7.23 (15)	4.68 ± 3.46 (24)
5	7.48 ± 4.01 (25)	6.08 ± 2.98 (11)	11.17 ± 5.61 (12)	4.18 ± 2.89 (18)
6	6.45 ± 3.88 (22)	6.35 ± 3.03 (10)	9.80 ± 5.23 (12)	....
7	5.37 ± 3.27 (18)	5.00 ± 2.43 (6)	9.62 ± 3.26 (9)	....

* Figures in parentheses indicate number of subjects.

TABLE 2.—*Days on Which Maximum Plasma Bilirubin Concentration Occurred*

	This Study				Hsia and Co-Workers [21]			
	Premature		Full Term		Premature		Full Term	
Day	No.	%	No.	%	No.	%	No.	%
1	..	..	..	...	1	7.1	..	....
2	3	15	1	9.1	2	14.3	15	62.5
3	6	22	3	27.3	3	21.4	7	29.2
4	7	26	3	27.3	6	42.9	2	8.3
5	8	29	..	...	2	14.3	..	....
6	1	4	3	27.3	..	...	..	....
7	1	4	..	...	..	...	..	....
8	..	..	1	9.1	..	...	..	....

Chart 2 compares plasma bilirubin values in the 27 prematures with the 12 term infants for the first 10 days. The range of values appears comparable for the two groups and there is no demonstrable tendency for the bilirubin concentrations in the term infants to fall along the lower aspects of the graph. On the contrary, they are well scattered throughout, and some prematures have considerably lower values than the more mature neonates.

The mean plasma bilirubin concentrations for premature and term infants for the first 10 days of life are shown in Table 1, together with similar data obtained by

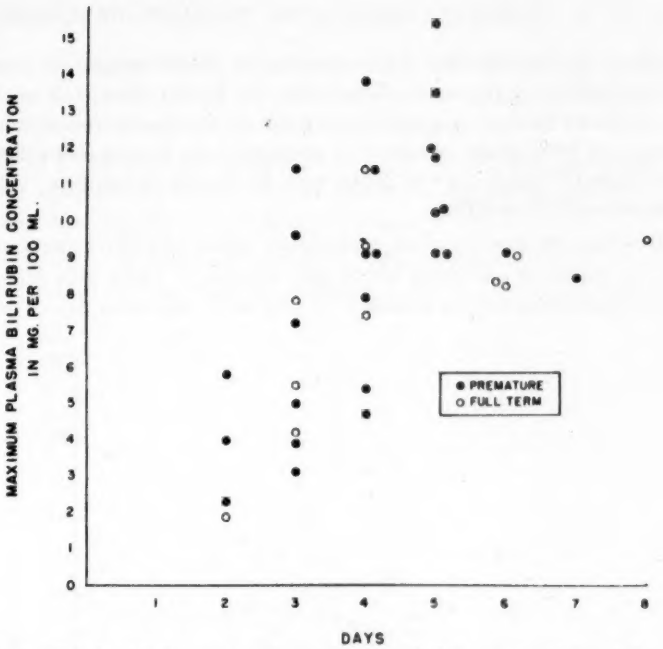

Chart 3.—Relationship between maximum plasma bilirubin concentration and day of occurrence.

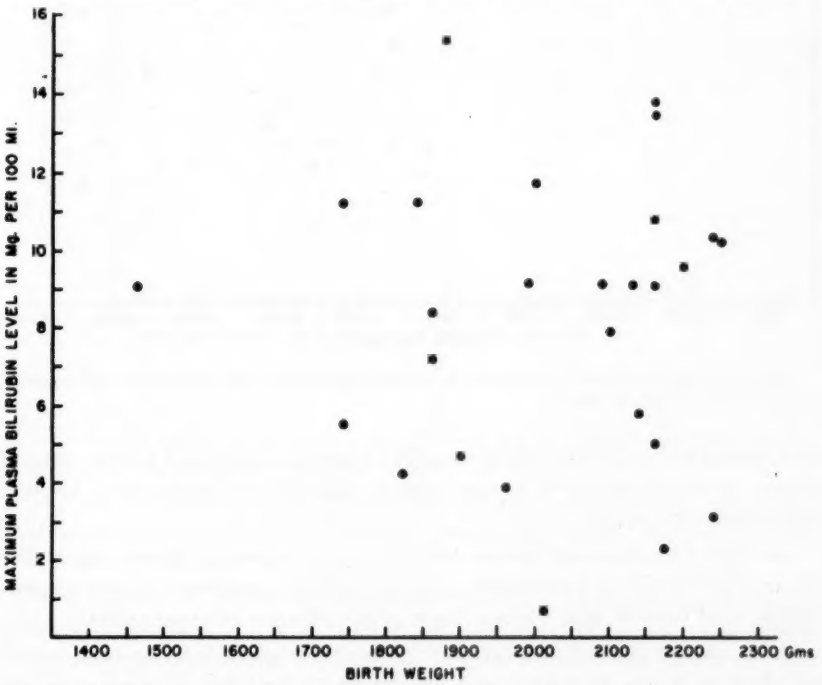

Chart 4.—Relationship of intensity of hyperbilirubinemia in prematures to maturity as measured by weight at birth.

Hsia.[21] On any given day, bilirubin values obtained for premature and for normal infants show no statistical differences. The values for P vary from 0.12 to 0.94. However, the mean for each day is consistently greater for the prematures. Comparison of the means for both groups of infants by summating the P values according to the method of Fisher [25] yields a χ^2 of 28.006 with 14 degrees of freedom. This is statistically significant ($P = 0.015$).

Table 2 illustrates the days on which a maximum plasma bilirubin concentration was achieved by infants in our series and in that of Hsia.[21] Those who failed to develop hyperbilirubinemia are not included. In our series, the mean day of maxi-

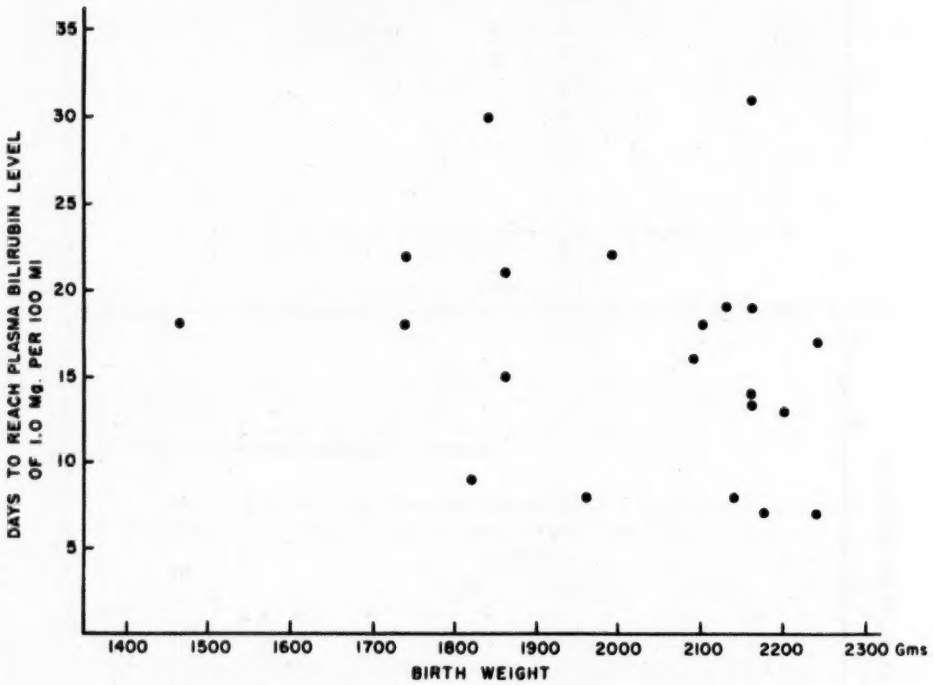

Chart 5.—Relationship between duration of hyperbilirubinemia in prematures and maturity as measured by weight at birth.

mum plasma bilirubin concentration was 4.0 for the prematures and 4.5 for the term infants. In Hsia's series,[21] the means were 3.4 and 2.6 days, respectively, for premature and term infants.

In Chart 3 the maximum plasma bilirubin concentrations are plotted against the day on which they were encountered. In general, higher maximum bilirubin concentrations tend to occur late, whereas lower peak values are achieved earlier.

In an attempt to correlate severity of the process responsible for neonatal hyperbilirubinemia in the premature with immaturity of the infant, maximum plasma bilirubin concentrations were plotted against weight at birth in Chart 4. No correla-

tion can be shown. Some prematures of low birth weight have lower maximum bilirubin values than those of higher weight, and variability is great within birth weight groups, as in the group of 2,100 to 2,200 gm.

Chart 5 shows the time required to reach a concentration of 1.0 mg. per 100 ml. plotted against birth weight. The distribution is almost identical with that shown in Chart 4, and again no correlation is evident.

In Chart 6 the maximum plasma bilirubin concentration for each premature is plotted against the time required to achieve a level of 1.0 mg. per 100 ml. There is a

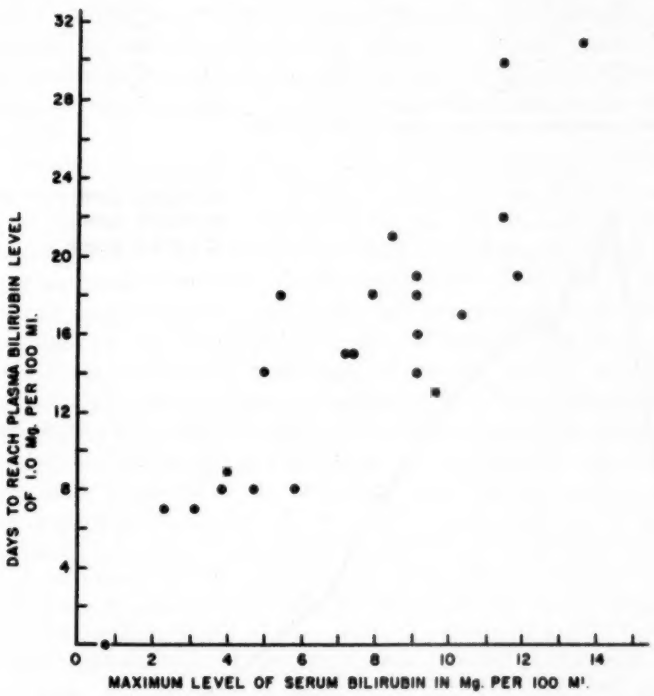

Chart 6.—Relationship between intensity and duration of hyperbilirubinemia.

tendency for the values to fall upon a straight line. From this graph it appears that the greater the hyperbilirubinemia, the longer is its duration.

In Table 3 it is seen that, of 23 prematures for whom complete bilirubin curves could be obtained, normal adult values were observed by the 22d day in 21, and all 23 were at this level by 32 days.

From Charts 1, 2, 4, and 5 it can be concluded that the degree of physiologic hyperbilirubinemia cannot be correlated with birth weight. This can be more clearly illustrated by an examination of individual bilirubin curves. The curves of three prematures are represented in Chart 7. Curves *B* and *C* are widely separated, although the birth weights are almost identical.

TABLE 3.—*Days Required for Plasma Bilirubin Concentration in Prematures to Fall to 1.0 Mg. per 100 Ml. or Less*

Day	No. Infants	Cumulative Totals
0	1	1 *
7	2	3
8	3	6
9	1	7
13	1	8
14	2	10
15	1	11
16	2	13
17	1	14
18	3	17
19	2	19
22	2	21
30	1	22
31	1	23

* Plasma bilirubin concentration never rose above 0.7 mg. per 100 ml.

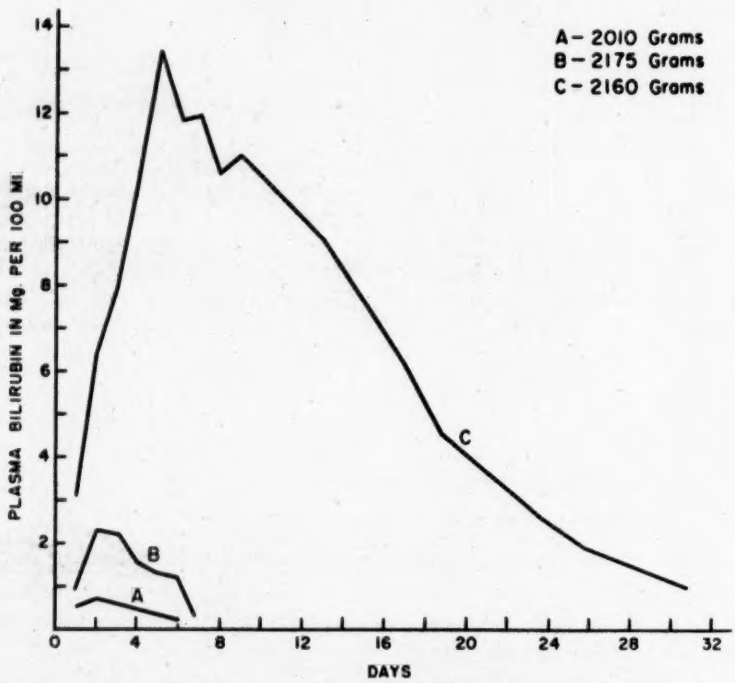

Chart 7.—Serial plasma bilirubin curves in three premature infants illustrating the variability of the intensity and duration of physiologic hyperbilirubinemia.

COMMENT

While the reported incidence of neonatal jaundice is rather variable—30% according to Waugh [26] and 80% according to Hirsch [15]—the occurrence of physiologic hyperbilirubinemia is more frequent, since plasma bilirubin levels may be elevated in nonicteric infants. Among our subjects, jaundice developed in 26 of 27

prematures and 10 of 12 normal newborn infants. The single nonjaundiced premature and one of the nonjaundiced term infants had no elevation of plasma bilirubin.

In term infants there is an early rapid rise in plasma bilirubin to a maximum concentration, followed by a slower decline to normal levels. The peak of the curve usually occurs between the second and the seventh day of life.‖ In this respect the findings in the prematures of our study are comparable to the published data on term infants. The mean times on which maximum plasma bilirubin concentrations occurred were almost identical in our premature and in our normal newborn infants, being 4.0 and 4.5 days, respectively. Waugh [26] found the peak of the curve on the fifth day. In Davidson's [10] series, the mean day for maximum bilirubin concentration was 3.1, with the largest group falling on the second day. The highest mean icterus index for 104 normal newborn infants reported by Bonar [17] occurred on the fifth day. Similarly, Snelling [6] found the peak on the fifth day. Hsia [21] found the highest bilirubin levels on the second day for term infants and on the fourth day for prematures.

Davidson, Merritt, and Weech [10] showed that the maximum bilirubin concentrations occurred later in those infants in whom the bilirubinemia was of severer degree. Larsen and With [18] also noted that the peak occurred earlier in nonicteric newborn infants. Essentially the same relationship between peak of the curve and day of occurrence is described here for prematures.

Among prematures no correlation could be established between the severity and duration of the bilirubinemia, on the one hand, and the birth weight, on the other. Using birth weight as an index of maturity, Bonar,[17] Schick and his colleagues,[19] Findlay and associates,[20] and Larsen and With [18] reached similar conclusions. As was demonstrated for normal newborn infants by Davidson,[10] the duration of hyperbilirubinemia in prematures is directly related to its intensity.

In 21 of 23 prematures for whom complete bilirubin curves were obtained a concentration of 1.0 mg. per 100 ml. or less occurred by the 22d day, and in the remaining 2 normal levels were present by the 32d day. Davidson [10] studied 57 term infants in whom bilirubin concentrations were followed until similar levels were reached. In 28, normal values were present by 20 days; in 12, between 20 and 30 days; in 8, between 30 and 40 days, and in 9, between 40 and 70 days. Thus, in 14 of these newborn infants hyperbilirubinemia persisted longer than in any of our prematures. In contrast to the above study, Findlay [20] found that a concentration of 1.0 of bilirubin per 100 mg. was present in all infants studied by 2 weeks of age, and Larsen and With [18] described normal levels occurring between 2 and 4 weeks of age.

The striking variability in neonatal hyperbilirubinemia among term infants was noted by Ylppö.[13] Larsen and With [18] also commented upon the pronounced individual differences in serial bilirubin curves. In their series bilirubin values varied from 1.0 to 50 mg. per 100 ml., with 17 infants having levels above 15 mg. This variability has also been demonstrated for our premature infants.

The only study of physiologic hyperbilirubinemia in prematures comparable to ours is that of Hsia, Allen, Diamond, and Gellis.[21] No statistically significant differences between the plasma bilirubin levels in prematures and term infants could be

‖ References 16 and 18.

shown in our study, although the mean bilirubin concentration of the first seven days is slightly but consistently higher in the prematures. A similar comparison between the two groups of infants in Hsia's series reveals no significant differences on the first and second days and highly significant differences on the fourth and fifth days. The bilirubin levels and the standard deviations of the mean in the two groups of term infants are comparable; in regard to the prematures, the bilirubin concentrations obtained by Hsia are higher to a degree that is statistically significant. The standard deviations for this group are considerably higher than in our series. We are unable to account for the differences between the two studies. It cannot be explained by the preponderance of Negro infants in our series. Comparison of the bilirubin values in our white prematures with those of Hsia's infants reveals similar differences between the two groups.

CONCLUSIONS

Whatever may be the mechanism responsible for physiologic hyperbilirubinemia, it is clearly established that it is initiated before birth, as shown by Ylppö [13] and Davidson, Merritt, and Weech,[10] who demonstrated an increase in bilirubin concentration in cord blood of term infants that correlated directly with the degree of postnatal bilirubinemia. However, Findlay and his co-workers [20] were unable to substantiate this. It would seem likely that any demonstrated association between cord-blood bilirubin concentration and the subsequent course of the bilirubinemia in term infants would be equally valid in the premature. Mitchell [16] noted no difference in cord-blood bilirubin between premature and term infants. On the other hand, Hsia, Allen, Diamond, and Gellis,[21] in a small number of prematures, found a mean concentration of cord-blood bilirubin of 1.2 mg. per 100 ml., as compared with a mean of 2.1 mg. per 100 ml. for term infants. Since these premature infants later had significantly greater values than the term infants, the relationship between cord-blood bilirubin and postnatal bilirubinemia is the reverse of that described by Ylppö [13] and Davidson.[10]

At first glance, one might anticipate that cord-blood bilirubin would be higher in prematures because of expected greater deficiencies in hepatic excretion. However, from the work of Schick,[27] Wagner,[28] and Williamson [29] on placental iron content, from the studies of Findlay, Higgins, and Stanier [20] on the differential serum bilirubin concentration in umbilical artery and vein, and from analysis of bilirubin content of meconium by Ylppö,[13] it would appear that the placenta is the organ by which fetal blood is cleared of bilirubin. Its concentration in cord blood is, therefore, a measure of placental rather than of hepatic function. A term infant, born when one may expect senescent placental changes to have begun, might well have higher cord-blood values, consistent with decreasing function, in contrast to prematures, born at a time when the placenta is operating more efficiently. As a matter of fact, Gottlieb and Kearns [30] have shown a higher incidence of jaundice in those newborn infants in whom the placentas showed greater degrees of degenerative changes. From unpublished data of the authors, blood taken during Caesarean section from uterine and antecubital veins of mothers at term failed to show any differences in bilirubin content. As yet, similar samples of blood from mothers considerably before term have not been obtained. One indication of greater placental clearance would be higher values in blood obtained from the uterine vein. However, it may be that, in view of the tremendous placental blood flow, the actual increment of bilirubin in uterine-vein blood may be too small to be detectable.

The demonstration in this study that there are no significant differences in plasma bilirubin concentration among individual premature and term infants challenges the concept that physiologic hyperbilirubinemia is a measure of fetal maturity. Other workers as well have failed to establish a positive correlation between bilirubinemia of the newborn and maturity as expressed by weight at birth. Indeed, some prematures show consistently lower values than some normal newborns.

The data reported in this communication do not substantially alter prevailing concepts concerning the pathogenesis of physiologic hyperbilirubinemia. However, the documentation that some prematures show considerably lower plasma bilirubin levels than some normal newborn infants challenges, perhaps, the preeminent role of maturity of the liver in the genesis of icterus neonatorum. Certainly one would have anticipated that hepatic function in the clearance of bilirubin would be more efficient in larger, and hence presumably more mature, infants. While the trend is in this direction in the two groups of infants, there are enough exceptions to focus one's thoughts anew on the mechanism of hyperbilirubinemia.

Certain theoretical considerations lead to the conclusion that bilirubinemia may be related to deficient formation of bile salts in early postnatal life. It is logical to begin with the biochemistry of bilirubin formation. Recent data would appear to show that the conclusion of Whipple [31] that the degradation of hemoglobin to bilirubin is stoichiometric is no longer tenable. By the use of radioactive glycine, Rittenberg and co-workers ¶ have established that not all bilirubin is derived from hemoglobin. Contrariwise, not all of the heme fraction of hemoglobin is converted to bilirubin, and other dipyrrole compounds may be formed instead.[34] Therefore, the amount of hemoglobin destruction cannot be assayed by a quantitative determination of excreted heme derivatives.[34] Also, since bilirubin is not derived exclusively from hemoglobin and since that portion which does come from hemoglobin may be very variable in amount, one may question whether bilirubin formation in the fetus is qualitatively and quantitatively different; perhaps greater amounts of bilirubin are formed, which are responsible for the elevated cord-blood concentrations. Part of the question has already been answered in the negative. A group of Canadian workers established that the ferroporphyrin fractions of fetal and adult hemoglobins are identical [35] and could demonstrate no correlation between neonatal bilirubinemia and the quantity of destruction of fetal or adult hemoglobin.[36] However, the entire question deserves more extensive investigation.

Hemoglobin, on release from red blood corpuscles, does not long remain free in plasma but is removed by the cells of the reticuloendothelial system, where much of its subsequent biochemical breakdown occurs. The first step appears to be the oxidation of the porphyrin fraction, leaving an iron-hemoglobin complex known as verdohemoglobin.[34] Iron is then removed, and further change of the heme fraction occurs, giving rise to biliverdin-globin which is, in turn, oxidized to bilirubin-globin.# The latter circulates in blood bound to the albumin fraction of plasma protein.[39] In the liver, the link to albumin is broken, globin is removed, and bilirubin is converted to a metal complex,[40] probably sodium bilirubinate, in which form it is excreted into the bile.[41] The precise mechanisms by which these changes are accomplished in the liver are unknown. It seems not unreasonable to postulate that

¶ References *32* and *33*.

References *37* and *38*.

bile salts may be necessary at least for the formation of sodium bilirubinate. Hess [42] has shown that very little or no bile can be obtained by duodenal drainage on the first day of life and that gradually increasing amounts appear on successive days. The absence of bile in the duodenum or its presence in small amounts is probably a reflection of deficient hepatic secretion, since antenatally there is no need for biliary secretion in the absence of intestinal digestion. Hess has estimated that it requires 7 to 10 days for biliary secretion and excretion to become established. Since removal of bilirubin from plasma may depend upon the action of bile salts, failure of bile production would predispose to retention of bilirubin.

SUMMARY

Daily serial determinations of bilirubin were performed in 27 premature and 12 term infants. All but one of the prematures and two of the term infants were jaundiced. Only the nonicteric premature infant and one of the nonicteric normal newborn infants failed to develop hyperbilirubinemia. For 23 of the prematures the bilirubin curves were followed until a level of 1.0 mg. per 100 ml. or less was reached. Only 2 of the 12 term infants could be so followed.

Among the prematures, there is a wide range of variability in plasma bilirubin concentration. Infants above and below 2,000 gm. showed no differences, and the distribution of the bilirubin values was similar in the two groups.

Bilirubin concentrations among individual premature and term infants show no statistically valid differences, although the term infants have consistently slightly lower mean values to a degree which is statistically significant. As a group, therefore, prematures show a slightly greater degree of physiologic hyperbilirubinemia, although there is considerable overlapping among the individual members of both groups.

The degree of bilirubinemia and its duration are not related to birth weight. In both premature and term infants, the greater the bilirubinemia the longer is its duration; the higher the maximum value the later is it achieved.

The mean day for maximum bilirubin concentration was 4.0. This compares with two to seven days found by various authors for term infants.

Of the 23 prematures for whom complete bilirubin curves were obtained, normal values of 1.0 mg. per 100 ml. were achieved by 22 days in 21 and by 32 days in all. From this study it cannot be concluded that the hyperbilirubinemia of prematurity is of longer duration than that of normal newborn infants.

It is possible that bile salts are necessary for the biochemical process whereby bilirubin is converted to sodium bilirubinate, in which form it is excreted. The deficient secretion of bile salts in the early postnatal period may be related to the meager intestinal digestive activity of this period. If bile salts are indeed required for the removal of bilirubin from the blood by the liver, then postnatal bilirubinemia is not a function of hepatic immaturity, but, rather, the expected result of an understandable physiologic mechanism.

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Case Reports

CONGENITAL ADRENAL APLASIA

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CONGENITAL aplasia of the adrenal glands has been noted previously to occur in cases of cranial anomaly, such as an encephalus or hydrocephalus, or other central-nervous-system malformations extensive enough to involve the pituitary gland. There have been cases of Addison's disease in adults in which at autopsy the adrenals could not be found.[1] Present knowledge of adrenal function would seem to indicate that the condition of these adrenals was acquired rather than present at birth. Selye states that it is doubtful that complete aplasia ever occurs and that it would be incompatible with postnatal life.[2] Acute or chronic adrenal insufficiency during the first year of life with the clinical features of either bronze pigmentation of the skin, gastrointestinal symptoms, or hydrolability, together with autopsy findings of adrenal pathology or successful adrenal replacement therapy, has been reported infrequently. There are seven such cases on record, with the earliest onset being on the seventh day of life.*

The following case is presented as an additional instance of acute adrenal insufficiency with bronzing of the skin and death at 24 hours and striking adrenal findings at autopsy.

The baby was the product of a full-term uneventful pregnancy in a healthy 28-year-old white woman, primipara and primigravida. The mother was Rh negative, but no antibodies were demonstrated on repeated testing. Labor was spontaneous in onset, of 17 hours' duration, and not difficult. Meperidine (Demerol) and secobarbital (Seconal) were used for analgesia, and the delivery was done under spinal anesthesia with employment of low application of forceps. The presentation was cephalic, and the respirations and cry were prompt and spontaneous; the color was good. The birth weight was 7 lb. 8 oz. (3,400 gm.) Upon examination the following morning at approximately 18 hours of age, the baby's reflexes, tone, and hydration were normal; the head, nose, throat, heart, lungs, and abdomen were entirely negative. The notation was made that the baby appeared "slightly jaundiced" and because of the mother's Rh history a blood work-up was ordered. Immediately after the finger puncture for the blood, the baby went into a shock-like state characterized by grayish cyanosis, shallow irregular respirations, slow weak pulse, and failure to respond to stimuli. The infant was placed in a positive-pressure air-lock, where there was a slight improvement in color. When the infant was removed for examination, there was not enough spontaneous respiratory effort to provide adequate oxygenation, and the cyanosis promptly deepened. There was air exchange in both lungs, the fontanelle was flat, and no cardiac murmurs were heard. Epinephrine and nikethamide (Coramine) were administered, but shortly after a brief episode of twitching of the extremities the baby died, 24 hours after birth. The laboratory results were as follows: RBC 6,190,000; Hgb. 17.7 gm. per 100 cc.; 16 nucleated RBC's per 100 WBC's; WBC 9,950, with PMN 29%, L. 65%, E. 6%; Rh-negative; Coombs's test negative.

* References 3-9.

Autopsy Report.—Gross: The body was that of a well-developed newborn baby girl of average size. The skin showed generalized bronze discoloration mixed with lividity.

There was a small caput of the scalp showing moderate edema and slight hemorrhage. Moderate congestion of the cortical vessels over the hemispheres was noted; however, hemorrhage was not present. The pituitary gland was normally located and showed no gross abnormalities.

The heart, lungs, and great vessels showed no significant pathological changes other than passive pulmonary congestion and moderate atelectasis.

The abdominal organs were entirely normal. The biliary tract permitted free expression of bile into the duodenum. Careful search of the right side of the abdominal cavity from the diaphragm to the pelvis revealed no adrenal gland. The left adrenal was found in the normal position and was approximately one-third the normal size, weighing 2 gm. The genitourinary organs were normal.

Microscopic: The glandular architecture and normal cellular pattern were completely disrupted. There was marked hypoplasia of the cortex, the cortical cells being atrophic and diminished in number. A definite fetal zone could not be delineated. Extensive hemorrhage in the medulla was noted.

COMMENT

This baby apparently had no functioning adrenal tissue and survived the delivery with the aid of maternal adrenal hormones, but at the first postnatal trauma, the finger puncture, died of acute adrenal insufficiency. Recent work by Klein, Fortunato, and Papadatos has demonstrated free blood corticoids in cord blood to be at adult levels, that of 2- to 5-day-old infants at very low levels, and those during the first 24 hours intermediate between these values. What was considered slight jaundice in this case may have been adrenal in origin, as it was definitely more bronze than yellowish in color, and none of the other common causes of jaundice in the first 24 hours was present.

SUMMARY

A living full-term normally developed baby girl is described who died at 24 hours with autopsy findings of bronze discoloration of the skin, absence of the right adrenal, and hypoplasia of the left. This would appear to be the earliest age at which such adrenal failure and pigmentation have been reported.

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EPIDERMOLYSIS BULLOSA HEREDITARIA LETALIS IN NEWBORN TWINS

Report of Two Cases with Failure to Respond Favorably to Cortisone

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ANCON, CANAL ZONE

EPIDERMOLYSIS bullosa is a chronic hereditary condition of the skin and/or mucous membranes, characterized by the development at any time of life, usually early, of vesicles or bullae under the influence of trauma. This disease occurs in varying grades of severity, from the fatal to the mildly symptomatic.

Cockayne [1] classified the condition into two main types, epidermolysis bullosa simplex and epidermolysis bullosa dystrophica. He subclassified the latter into the dominant form, the recessive form, and the types originally described by Guy and Wende, the "typhus maculatus" type described by Mendes da Costa and van der Valk, and the type described by Heinrichsbauer.[5]

Herlitz [2] first named and collated cases of a distinct fatal type which he called "epidermolysis bullosa hereditaria letalis," including 8 of his own cases and 14 others, those of Mautner,[3] Jenny,[4] Heinrichsbauer,[5] and Kuse.[6]

Herlitz stated that epidermolysis bullosa hereditaria letalis appears at birth or shortly thereafter. It is recessive in inheritance, the formation of bullae is progressive, and death usually supervenes before the third month.

Lamb and Halpert [7] added another case of their own and collected the cases of Davidson,[8] Brandberg,[9] Schroder and Wells,[10] and the case reported by Black, Wilhelm, Gilbert, and White.[11] According to Lamb and Halpert, their case was the 27th recorded.

Matheson and Rosner [12] and, later, Schäffer [13] reported one and two cases, respectively. Schäffer stated that only 27 cases had previously been reported, apparently not including the case of Matheson and Rosner.

Kagen, Williams, Giffin, and Wiley [14] subsequently reported two cases, one of which lived to the age of 16 months, but which, because of its clinical appearance and course, undoubtedly belongs in this series.

Escardó and Trepat [15] reported the disease in twins, male and female, with death from bronchopneumonia in the male. It was noted, however, that the father of the twins had epidermolysis bullosa, indicating the dominant transmission of the disease in these cases. The bullae of the male infant cleared completely on one occasion at least prior to death.

As the cases described by Herlitz [2] were recessive in nature and progressive, this case is deemed not to meet the criteria of Herlitz' cases, and therefore is not included in this series.

REPORT OF CASES

CASE 1.—A mulatto Panamanian girl was delivered spontaneously by cephalic presentation, at Gorgas Hospital, Ancon, Canal Zone, on March 13, 1953. She was the first of twins, the second of which was born 18 minutes later (Case 2). Birth weight was 5 lb. 5½ oz. (2,425 gm.), and total length was 49 cm. The cry was lusty. It was noted that there were denuded areas of skin on the thumb and the index, middle, and small fingers of the right hand, the thumb and index finger of the left hand, and on the knees and ankles. The thumbnails were long, lusterless, and onychogrypotic. This infant was seen by one of us (L. S. L.) later that day, and a diagnosis of epidermolysis bullosa of the recessive dystrophic type was made.

Course in the Hospital.—There was a progressive increase in the number of large flaccid bullae with subsequent denudation of large surfaces of the body. The temperature rose above normal on the fifth day, reaching a peak of 103 F. on April 25, 1953. New bullae appeared daily, and an ulcer appeared in the center of the hard palate. The Nikolsky phenomenon could not be elicited.

Laboratory Data.—The red blood cell count varied between 5,150,000 per cubic millimeter on March 16 and 1,940,000 per cubic millimeter on April 18, rising after whole blood transfusions to 3,700,000 per cubic millimeter on April 24.

The white blood cell count varied between 4,500 and 11,650 per cubic millimeter. The differential count was not remarkable.

Cultures from unruptured bullae on March 25 were positive for Bacillus proteus and Pseudomonas aeruginosa. On April 4, cultures from unruptured bullae were positive for Staphylococcus aureus (hemolytic), coagulase positive.

Urinalysis for porphyrobilinogen on March 16 was positive.

Blood was Group O Rh +.

On March 19, total protein was 4.83 gm. per 100 cc. (albumin 3.65 gm. and globulin 1.18 gm.).

On March 20, total protein was 4.57 gm. per 100 cc. (albumin 3.17 gm. and globulin 1.40 gm.), serum glucose 90 mg. per 100 cc., and serum chlorides 620 mg. per 100 cc.

Treatment.—Ten milligrams of vitamin K was administered intramuscularly at birth.

On March 14, 500 mg. of ascorbic acid was added to the total daily formula. Penicillin procaine, 150,000 units twice daily intramuscularly, was started on March 18 and continued until death.

Cortisone, 5 mg., was administered intramuscularly twice daily from March 28 to April 2, when it was discontinued because of lack of favorable response. A whole-blood transfusion of 60 cc. was given on March 17, and 60 cc. was given on March 18.

The patient died on April 26, 1953, 44 days after birth.

Report of Autopsy.—The infant was a well-developed mulatto girl, 49 cm. long, weighing 2,550 gm. Nutrition was poor, and on the skin were multiple bullae with denudation of the epidermis over the bony prominences, the abdomen, and the neck, with small hemorrhages in the dermis beneath the bullae.

A large amount of thick whitish mucoid material partially plugged the lumen of the trachea, with an estimated 60% occlusion. The thyroid and thymus glands weighed 3 gm. each. The heart weighed 18 gm. and showed a patent foramen ovale. The pleural cavities contained no fluid. The lungs were normal. The adrenals weighed 8 gm., the spleen 10 gm., the pancreas 8 gm.; all were grossly normal. The liver showed passive congestion. The kidneys together weighed 30 gm. and were grossly normal. All other organs were grossly normal. The linings of the trachea, esophagus, and gastrointestinal tract were normal. The subcutaneous tissues and bones were yellow. This was not reflected in the sclerae, skin, or mouth.

Microscopic Examination.—This was made of the brain, thyroid, salivary gland, heart, lung, liver, spleen, pancreas, adrenal, kidney, and skin. All were essentially normal except for the lungs and skin. In the lungs the capillaries were acutely congested, and there was moderate alveolar hemorrhage. There were numerous macrophages in the alveoli. The walls of the small bronchi showed a minimal chronic inflammatory reaction.

In sections of the skin which were not involved grossly, the epidermis was of average thickness, and the various layers appeared normal. The basal layer was pigmented. There was a fine vacuolated space between the epithelium and the immediate subadjacent dermis, which was fairly constant. This was present also in the epithelial linings of the hair follicles and sweat ducts.

Elastic-tissue stain (Weigert's) of the skin were done. In the papillary layer of the dermis there was a moderate number of fine elastic fibrils, which was diminished in some areas. In the deeper dermis, there were plentiful, thicker, and apparently normal elastic fibrils. On hematoxylin-and-eosin stain of the skin there appeared to be a fairly constant basophilic degeneration of the collagen of the dermis.

Fig. 1 (Case 1).—Appearance at 14 days after birth.

Anatomic Diagnosis.—Tracheal obstruction, partial; acute pulmonary congestion; bronchitis, chronic minimal; patent foramen ovale; jaundice; acute passive congestion of liver; anemia (clinical); emaciation; skin, epidermolysis bullosa.

CASE 2.—A mulatto Panamanian girl was delivered by breech extraction 18 minutes after the birth of her identical twin, at Gorgas Hospital, Ancon, Canal Zone, on March 13, 1953. There was delayed cry and respiration. Birth weight was 6 lb. 4 oz. (2,835 gm.). It was noted that there was a denuded surface of skin over the left temple, on the posterior surface, on the distal third of the right leg, and at the base of the umbilical cord. Later that day a diagnosis of epidermolysis bullosa of the recessive dystrophic type was made.

Course in the Hospital.—The day after birth denuded areas appeared on both knees, the right anterior chest, both lips, the right deltoid region, and on the hips and buttocks. Alveolar ridge

lesions developed later. Thereafter, new lesions developed continually as large flaccid bullae followed by denudation of the epidermis. The infant, as did her twin, fed well. On April 1 a systolic murmur was noted at the apex of the heart.

The temperature rose above normal on the fourth hospital day and reached a peak of 103 F. on March 29, gradually dropping to 99 F. on April 3, 1953. The Nikolsky phenomenon could not be elicited. By March 24, the back and buttocks were entirely denuded of epidermis.

Laboratory Data.—Cord Wassermann and Kahn were negative. Blood was Group O Rh +. The WBC count varied between 5,800 and 12,450 per cubic millimeter, and the RBC count from 4,570,000 on March 16 to 2,250,000 per cubic millimeter on March 30.

Fig. 2 (Case 2).—Appearance at 14 days after birth.

Urine specimen was inadequate for porphyrobilinogen determination.

On March 30, the serum chlorides were 616 mg. per 100 cc., the serum glucose 110 mg. per 100 cc.

Total protein 4.59 gm. per 100 cc. (albumin 3.33 gm. and globulin 1.26 gm.).

Therapy.—At birth the infant received 10 mg. vitamin K intramuscularly. Cortisone, 5 mg. every eight hours intramuscularly, was started on March 21 and continued until April 3, the day of death. Penicillin procaine, 150,000 units intramuscularly, was given every 12 hours from March 18 to March 23. Elixir oxytetracycline (Terramycin), 0.5 cc. q. 6 h., was started on March 30 and continued to death. On March 14, 500 mg. of vitamin C was added to the total daily formula. On April 1 the daily ascorbic acid dosage was reduced to 200 mg. The infant died on April 3, 1953, 21 days after birth.

Report of Autopsy.—The infant was a well-developed mulatto girl, 49 cm. in length, and weighed 2,675 gm. Nutrition was poor. The skin presented the main pathology. Approximately 50% of the epidermis had been sloughed off. The exposed corium was fairly clear, but there were small areas on the legs which were covered by a pyogenic material. All of the toenails and fingernails were deformed, and there was hemorrhage under and around these structures. The soles and palms were not grossly involved. Large areas over both calves and the anterior surface of the thighs were denuded. The back was particularly involved. There was no epidermis from the ischial tuberosities to the belt line, and there were bullae on the shoulders, chest, and abdomen. There were denuded areas over the extensor surfaces of the hands, feet, fingers, toes, cheeks, and right temple. There were several hemorrhagic infected areas involving the gums and the roof of the mouth.

The whole skin appeared edematous, and the epidermis was easily detached from the corium. The eyes, ears, nose, and throat were grossly normal. The thymus was small and fibrous on section. The lungs were markedly congested, but there were no petechial hemorrhages. The bronchi were free of exudate. There was a moderate amount of atelectasis present in both lungs. The heart was essentially normal.

There were no lesions grossly of the liver, kidneys, adrenals, or spleen. The gastrointestinal tract was patent. The mucosa was not remarkable. There was very little adipose tissue present.

Microscopic Examination.—The thyroid was normal. The trachea was edematous, and there were small vesicles beneath the basal layer of the epithelium, with separation of the epithelium similar to the lesions seen in the skin. There was marked atrophy of the lobules of the thymus due to diminution of the numbers of lymphocytes. There was a relative increase in the numbers of Hassall's corpuscles and eosinophiles and considerable fibrosis of the parenchyma. The heart was normal. There was a moderately severe atelectasis and moderately severe capillary bed congestion in the sections of lung. Most of the alveoli were filled with foamy macrophages.

There was moderate congestion of the sinusoids of the liver. The epithelium of the bile ducts was separated by small vesicles from the subepithelial connective tissue. The pancreas showed small vesicles beneath the duct epithelium. The acini and islets were normal. There was some hyperplasia of the lymph nodes with dilatation of the sinusoids and moderate reticulum cell hyperplasia. However, there were no lymph-node follicles, and there was a marked decrease in the number of lymphocytes. Sections of spleen, gastrointestinal tract, adrenals, kidney, and urinary bladder were normal.

The sections of apparently intact skin showed numerous small vesicles occurring singly and in chains. When occurring in chains, the vesicles were separated by thin septa which took a deep basophilic stain. This basophilic staining material was found also at the base of the vesicles, that is to say on the surface of the dermis, but did not involve the top of the vesicles at the basal layer of the epidermis. This basophilic staining tissue appeared to be degenerating collagen fibrils. There was marked fibroblastic proliferation with formation of new capillaries under the large bullae only. A few chronic inflammatory cells were present, but inflammation was never prominent except in those areas where epithelium had been lost.

There were vesicles beneath the basal epithelium of the sebaceous-gland ducts and the sweat gland ducts. As evidence that these were not artefacts, the peculiar basophilic degeneration of the collagen was also seen, particularly in the region of the hair follicles and sebaceous glands.

Elastic tissue stains of skin showed definite lack of elastic tissue in the upper dermis and in the dermal papillae. This deficiency was most marked about the hair follicles and sweat glands.

Anatomical Diagnosis.—Epidermolysis bullosa dystrophica, very severe; thymus, marked involution, due to cortisone administration; lungs, marked congestion; trachea, submucosal vesicles (probably artefact); liver, moderate congestion; bile ducts, submucosal vesicles (probably artefact); pancreas, submucosal vesicles (probably artefact); pyoderma, secondary.

FAMILY HISTORY

In 1952, the mother of these twins, an apparently healthy, 29-year-old Panamanian mulatto, gave birth to a baby boy with what the mother and father describe as "the same disease as the twins have." That infant had denuded skin areas at birth, developed new bullae daily, and died on the 19th day after birth. The final diagnosis at the hospital in Panama, Panama, where he had been treated, was pemphigus neonatorum.

The mother had a normal 8-year-old girl by another marriage, and the father, an apparently healthy 30-year-old Panamanian mulatto, had a normal 11-year-old boy by a previous marriage.

There was no history of consanguinity, nor was there any history of a vesicular or bullous disease in either family.

COMMENT

The recessive nature of this condition is fully established in these cases because of the fortuitous family history in which both apparently normal parents have had normal children by other spouses, no normal offspring together, and no family history of epidermolysis bullosa.

In Herlitz's cases also, there were no family histories of epidermolysis bullosa. It appears that there will very occasionally be a mating of two persons, each carrying a recessive defective gene, who, though not apparently consanguineous, will consistently produce offspring with epidermolysis bullosa hereditaria letalis and when mated with one not carrying the defective gene will produce normal offspring.

All rational treatment for this condition, including in these cases cortisone, vitamin C, penicillin, oxytetracycline, topical bacitracin, blood transfusion, and adequate nursing care, have failed absolutely to alter the disease favorably.

It appears from the necropsy in one of these cases that the dermal collagen may participate in the disease process. There is no logical reason to suppose, considering the nature of this disease, that any therapy known up to this time will favorably alter the basic pathology.

The presence of bullae appearing at birth, in the absence of syphilis, should in our opinion point primarily to the diagnosis of epidermolysis bullosa, especially when nail deformities and mucous-membrane lesions are present or occur subsequently.

Porphyria is consistent with the diagnosis of epidermolysis bullosa.[16]

SUMMARY

Two cases of epidermolysis bullosa hereditaria letalis (Herlitz) occurring in twin mulatto females are reported.

These are the first cases of this malady reported in identical twins.

The parents of these twins produce abnormal offspring together, but with other mates produce normal infants.

Cortisone, penicillin, oxytetracycline (Terramycin), vitamin C in large doses, and blood transfusions failed to alter the condition favorably.

These are the 33d and 34th of these cases reported.

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MALIGNANT RETICULOENDOTHELIOSIS (LETTERER-SIWE DISEASE)

Report of Case with Normocholesteremic Lipid Granulomatosis and Eosinophilic Granuloma

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AFTER the publication of cases of eosinophilic granuloma of the skin, osseous forms, either solitary or multiple, began to attract the attention of clinicians in their attempt to find the relationship among the lipidoses, acute infective reticuloendotheliosis, and eosinophilic granuloma. We had the chance to study a very interesting case with fatal outcome in which biopsies and postmortem examination were possible, which gave a clue to two other cases of malignant reticuloendotheliosis published in 1950.

REPORT OF CASE

C. Kr., a girl, the second child of healthy parents without any hereditary trait or constitutional anomalies, was born after an uneventful pregnancy and parturition with a weight of 3,200 gm. The first child was a boy who had convulsions after sunstroke and suffered from attacks of bronchitis. Our patient was breast fed for a month, then artificial feeding was necessary. She thrived marvelously on acid milk (Karnemelk), and at the age of 5 months her weight was 7,190 gm.

While the first child, the boy, always showed a spotless skin, our patient, the girl, suffered very soon after birth from "eczema." The dermatologist's treatment was unsuccessful, but the parents did not care very much because the child did not suffer from itching, infection, or anything else.

One of us (D. P. R. K.) saw the baby at the age of 5 months because the "eczema" appeared and disappeared periodically but remained at the same site between two parallel lines encircling the body over the nipples and the last ribs. The skin affection existed again some weeks later; we saw yellow-brown monomorph papules covered with a fatty crust adherent to the skin. Slight swelling of the lymph nodes in the axillae existed, otherwise the child seemed a normal baby without intertrigo, hepatomegaly, or splenomegaly. With light pressure on the skin we saw a yellow underground in the papules, and the idea of a xanthomatosis of the skin arose. It was impossible to obtain the permission for a skin biopsy because of lack of serious symptoms and because the dermatologist's diagnosis seemed right to the parents. Between the 6th and 10th months an obstinate anorexia and dystrophy forced the parents to ask our advice. We now found a characteristically neuropathic baby with a new skin eruption of the same type of papules seen earlier. We were authorized to do skin biopsy, and we sent the skin slide to Professor Deelman, pathologist in Amsterdam University, who found nothing significant.

At the age of one year the child's weight had increased to 8,570 gm., and she had two teeth; now the skin was distinctly worse. The original site was crowded with the same yellow-brown papules, leaving no normal skin between them; on pressure the stain was not yellowish as before, but darker brownish. A second skin biopsy was done and examined by one of us (R. R. R.), who found only slight hyperkeratosis. It was now obvious that the lymph nodes were enlarged (axillae, neck, inguinal folds). We took the child into our department to study her condition properly.

Laboratory studies revealed the following: Mantoux test 1:100, negative; Bordet test, negative; Wassermann test, negative; red blood cell count, 3,700,000; hemoglobin, 11.2 gm. per 100 cc.; white blood cell count, 9,000; differential count, eosinophiles 1%, basophiles 1%, juveniles 1%, polymorphonuclear leucocytes 47%, lymphocytes 47%, and monocytes 3%; erythrocyte sedimentation rate, 32 mm. in one hour; vitamin A, 4 I. U., and carotene, 7 γ per 10 cc. of serum; cholesterol, 164 mg. per 100 cc., with 85% cholesterol esters.

In the hospital we found for the first time fever, otitis purulenta duplex, and doubtful mastoiditis. With penicillin therapy and paracentesis the child improved, but the skin now presented purpuric spots in the former "xanthomatous" skin, leaving a brownish pigmentation behind (Fig. 1).

The baby began to cough like one suffering from whooping cough; the x-ray, cough plate, and blood examination did not confirm our fear. The otologist thought the tonsils and adenoids, which were distinctly swollen, gave the stimulus for the cough, and ectomy was done with remarkable results which lasted only a few days. The child grew anemic, and blood examination revealed the following: hemoglobin, 8.7 gm. per 100 cc.; red blood cell count, 3,900,000; white

Fig. 1.—Skin with purpuric spots in the former "xanthomatous" skin.

blood cell count, 15,600; differential count, eosinophiles 2%, juveniles 3%, polymorphonuclear leucocytes 29%, lymphocytes 65%, and monocytes 1% (2 normoblasts). The blood was found to be Rh positive, Type A. The patient was doing well after transfusion of 100 ml. of blood and administration of chloramphenicol. The child improved so much that she could leave the hospital. Her weight was 9,800 gm.

Just a month later the baby suffered from a large "tumour" of the right scapula with fever and pain. Blood examination showed the following: white blood cell count, 16,000; differential count, eosinophiles 0%, basophile 1%, juveniles 10%, polymorphonuclear leucocytes 44%, lymphocytes 43%, monocytes 2%, and erythrocyte sedimentation rate, 35 mm. in one hour. No germs could be found in the blood culture. The x-ray showed a right scapula destructed by multiple cysts with sharp borders. The whole bone seemed enlarged, but the joint and soft parts were normal. In other visible bones no cysts or destruction could be found, but the lungs presented a pseudomiliary picture (Fig. 2).

The Mantoux test 1:100 was still negative, and the stomach contents were free from Koch's bacillus. We feared either a pseudomiliary Staphylococcus pneumonia with a central bone abscess or a generalization of eosinophilic granuloma. Treatment by means of administration of chloramphenicol followed by chlortetracycline was unsuccessful. The anemia progressed, with the blood examination showing the following: hemoglobin, 8 gm. per 100 cc., red blood cell count,

3,500,000, and white blood cell count, 18,200. We proposed surgical therapy. The surgeon found material which seemed to be "pus bonum et laudabile." We could not find any bacteria; the culture remained sterile. Our pathologist (R. R. R.) examined the material and diagnosed "eosinophilic granuloma" because the material consisted of a tissue rich in cells which were rather large with round or irregularly indented nuclei. In the midst of these cells an enormous number of eosinophilic polynuclears, multinucleated giant cells, some macrophages, and sporadic foam cells were detected; in some places necrosis was seen.

After the bone cysts were curetted, a new transfusion improved the body condition. A week later the blood contained 10.4 mg. calcium per 100 ml. and 142 mg. cholesterol, with 77 mg.

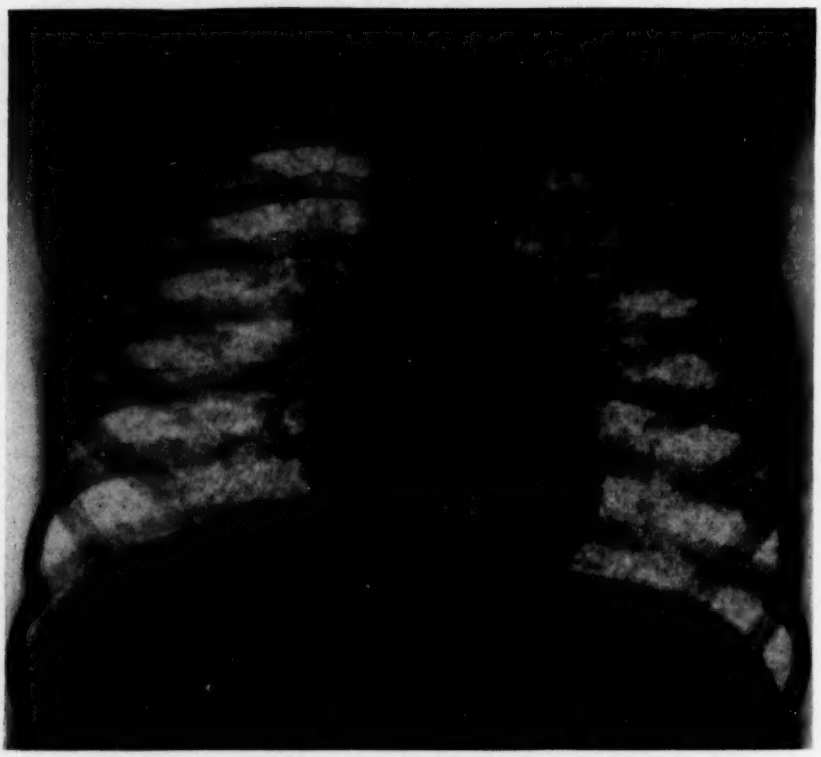

Fig. 2.—Pseudomiliary aspect of the lungs and multiple "cysts" in the right scapula.

cholesterol esters. The whole skeleton was examined by means of x-rays, but no other cysts were found.

Marrow biopsy was done when the blood examination showed the following: white blood cell count, 9,400; differential count, eosinophiles 0%, basophiles 0%, juveniles 11%, polymorphonuclear leucocytes 44%, lymphocytes 42%, and monocytes 3%; erythrocyte sedimentation rate, 44 mm. in one hour.

Marrow biopsy was controlled by the hematologist de Vries and showed rather active myeloid reaction with fewer eosinophiles than normal.

We tried now by means of corticotropin (ACTH) therapy to stop progress of the pathologic process. On Dec. 15th we began therapy with a dosage of 1 mg. corticotropin 4 times every 24 hours for 5 days and then 10 mg. per day. After a week the blood examination showed the following: white blood cell count, 24,400; differential count, eosinophiles 1%, juveniles 10%,

polymorphonuclear leucocytes 49%, lymphocytes 38%, and monocytes 2%. The blood pressure increased to 140 to 150 systolic and 100 diastolic. The general condition was much better—anorexia was over, the skin looked normal, and the weight increased.

A fortnight later the hemoglobin value had increased to 14 gm. per 100 cc. and the red blood cell count to 4,000,000, while the erythrocyte sedimentation rate was 11 mm. in one hour. The blood presure was 160/115 and the blood sugar value before meals was 97 mg. per 100 cc. The findings on electrocardiogram were normal, but those on x-ray of the lungs and scapula remained unchanged.

Jan. 7, 1952, the patient left the hospital. Her weight was 10,400 gm.; skin, practically normal; blood pressure, 110/60; white blood cell count, 17,000; differential count, eosinophiles 0%, basophiles 0%, juveniles 13%, polymorphonuclear leucocytes 47%, lymphocytes 37%, and monocytes 3%. At home the baby was given 2 mg. of corticotropin every 24 hours for 1½ months.

Then the baby entered the hospital again with a high temperature of 39 C. (102.2 F.), orthopnea (60 per minute), cyanosis, and bronchopneumonic infiltrations. The blood examination

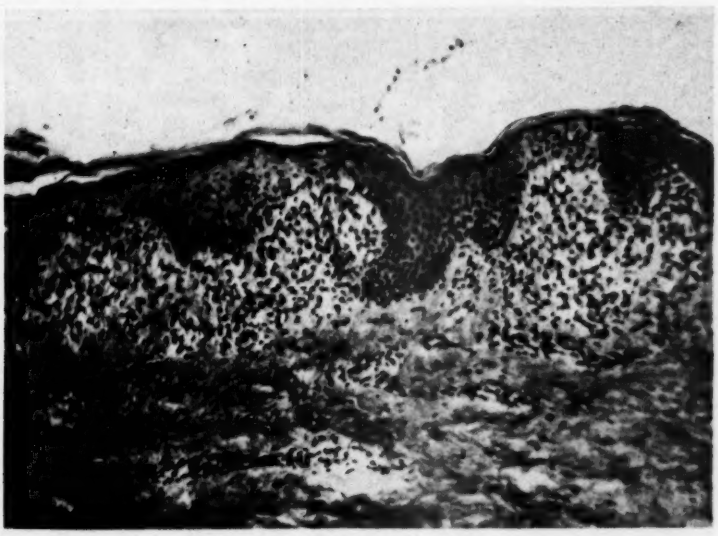

Fig. 3.—Skin with nests rich in cells.

showed the following: hemoglobin, 12 gm. per 100 cc.; red blood cell count, 3,900,000; white blood cell count, 16,600; differential count, eosinophiles 2%, basophiles 2%, juveniles 8%, polymorphonuclear leucocytes 52%, lymphocytes 33%, and monocytes 3%; erythrocyte sedimentation rate, 30 mm. in one hour. The findings on x-ray of the lungs and bones were unchanged, and the skin now showed a typical purpuric aspect (trunk, skull). A new skin biopsy was done, and Professor Ruiter, dermatologist in the Groningen University, examined the slides and sent some pictures. He found just below the epidermis regions rich in cells; these regions were strictly limited (Figs. 3 and 4). This granulation tissue was built up by histiocytic reticulum cells, mostly with large irregular round, oval, or indented nuclei. No mitoses were found and only rarely a foam cell. This granulation tissue showed edema, causing a rupture of the cells united only by protoplasm protrusions. Small widely opened blood vessels were numerous, with local hemorrhages. Next to histiocytic elements, round cells and some leucocytes, but no eosinophiles, could be found. A second marrow biopsy showed full activity with myeloid reaction and juvenile cells, normal erythropoiesis, normal relation between red and white elements, no distinct activity of reticular elements, and no increase of eosinophilic elements (de Vries).

The Thorn test had remained positive, but the body condition deteriorated steadily. The child's weight decreased to 9,200 gm., cyanosis was severe, and orthopnea reached 70 per minute;

the purpuric state was diminished. Blood examination showed the following: white blood cell count, 19,400; differential count, eosinophiles 1%, basophiles 1%, juveniles 7%, polymorphonuclear leucocytes 61%, lymphocytes 24%, monocytes 6%; platelets, 200,000 per cubic millimeter.

A new swelling of the right scapula needed treatment, and now nearly the whole scapula had been scraped out. The material examined by one of us (R. R. R.) gave the same microscopic aspect as formerly. A chemical analysis of this material revealed the following: lipids 3.1%, cholesterol 1.4%, cholesterol esters 0.7%.

In a very short time the general condition became poorer, and hepatomegaly and splenomegaly, general swelling of the glands, and a new purpuric condition developed. The mouth and exterior genitals remained free. Shortness of breath was so severe that oxygen had to be given continuously.

On Feb. 17 we treated the right scapula by means of x-ray without any success. The blood condition necessitated new transfusions. April 21 the patient died.

Partial autopsy was permitted.

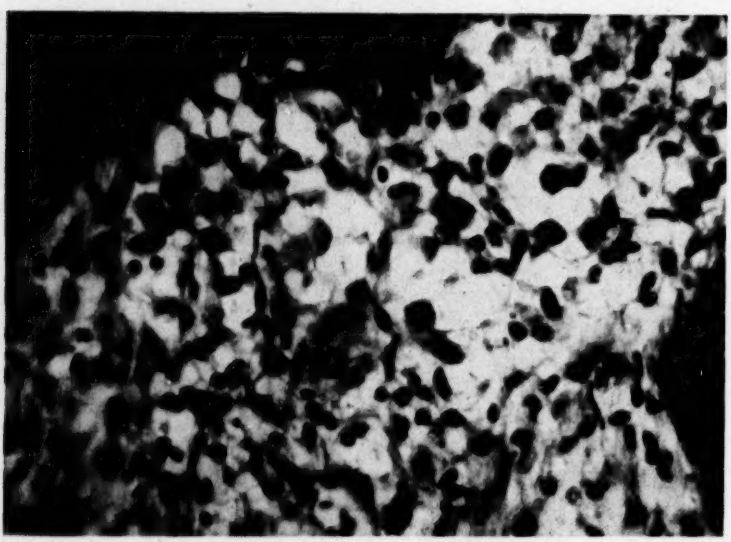

Fig. 4.—Slide of skin with larger magnification. Histiocytic reticulum cells with different nuclei and edema.

The body was extremely emaciated and covered from head to feet by purpura. General swelling of the glands and the cicatrices of the biopsies and operations was seen. When the chest was opened, the lungs did not collapse, and the diaphragm was low. The region of the thorax and the abdomen was normal. The thymus had changed into a hard mass grown together with the pericardium and the large vessels. In the pericardium a teaspoonful (4 to 5 ml.) of nonturbid liquid was found. The surface of the heart and the pericardium were moist and glistening. The heart weighed 77 gm.; the left ventricle was contracted and empty. The other cavities contained dark red blood with coagula. The valves were intact and thin. The wall of the left ventricle was 0.75 cm. in thickness, the right ventricle, 0.5 cm. The ductus arteriosus Botalli and the foramen ovale were closed.

The lungs were large, heavy, and solid; the left lung weighed 235 gm. and the right lung, 235 gm. The lower lobe of the right lung was covered by transparent connective tissue. The surface was glistening and smooth. Through the transparent pleurae yellow-white-colored foci ranging in size from that of hempseeds to that of peas could be seen. These foci were coalesced to form large irregularly shaped nidusses with indistinct borders. The trachea and bronchi were empty; the mucosa was smooth and yellow. The hilar nodes were large as peas; on section the

color was yellow-white. The lungs showed on section yellow-white hard irregularly formed granular foci with indistinct limits, ranging in size from that of a pea to that of a marble; the other parts of the lungs seemed normal. The spleen weighed 30 gm.; the capsule was smooth; on section the spleen was dark red without typical structure. The pulp was not soft. The liver weighed 430 gm. and had a smooth capsule. On section the color was yellow-brown and the structural details were poor. The portal vessels, the gall bladder, and the ducts were normal.

The kidneys together weighed 73 gm.; the surface was lobulated and smooth. On section the structure was normal; the renal pelves and ureters were normal, as were the adrenals. The stomach and esophagus were normal, and the duodenum, the ileum, and the colon showed nothing significant. The plaques of Peyer were not swollen, and the mucosa was smooth. In the mesentery we found numerous nodes which were as large as beans and yellow-white on section. The pancreas, the aorta, and the vena cava were normal. The nodes along the vertebral column were not swollen.

The macroscopic findings are summarized as follows: numerous yellow-white rather hard irregularly formed foci in both lungs; the thymus changed into a consistent mass; swollen nodes in the mediastinum and the mesentery as large as beans with adherances, and right-sided hypertrophy of the heart.

The microscopic findings were as follows: The lungs were completely changed; in only a few regions was the alveolar structure still present. The interstitium had increased in the form of foci which pressed the alveoli together; it was built up by fibroblasts and reticulum cells with some lymphocytes and a rare eosinophile. The reticulum cells were variable in dimensions; a few were very large, with two or more nucleoli. The nuclei were round, oval, or indented, with a tenuous chromatin structure and often with distinct nucleoli. The protoplasm was tenuous and weakly stained; syncytial structure was present. The conjunctive fibrils were present in the slides stained in the manner of Van Gieson. In the midst of the interstitial tissue were found some cysts and ducts covered by cuboid epithelium. Some alveoli were filled with very large foam cells. When studied in polarized light and stained with Sudan III they showed double refracting lipids. These foam cells were also seen in the interstitial tissue. In some parts this tissue was rich in overfilled vessels.

The spleen had an apparently normal structure, with follicles and interstitial tissue. In studies done by means of greater enlargement, reticulum cells were shown to be increased in the pulpa; these cells were floating unfixed, some extremely large with irregular indented nuclei. Proliferations in batches were not present. The pulpa was filled with blood, and there were some hemorrhages here and there. The sinuses were collapsed; only a few contained red cells, and some shed epithelial cells. The endothelium of the sinuses was slightly swollen. Foam cells were absent, and in polarized light no lipids could be found.

The mesenteric lymph node retained its normal structure, but numerous batches of proliferated reticulum cells which looked like Boeck's sarcoid were present, partly filling up the sinus, partly situated in the pulp strands. Some batches contained only a few cells, other batches were large and irregularly formed. Some reticulum cells had two or more nuclei; these were round, oval, and often indented, sometimes capriciously formed with one and sometimes more nucleoli. The nuclei were surrounded by a large poorly stained protoplasma zone. Syncytial connection was distinctly visible in many places. No double-refracting lipids were visible in slides stained by means of Sudan III.

The hilar lymph node retained normal structure; the nodes were edematous. There was a distinct sinus catarrh, and here and there proliferations of reticulum cells were present. Lipids were absent.

The thymus tissue was changed into connective tissue, being rich in cells in some places and fibrous in other places. Diffusely spread in this tissue seats of lymphoid cells were found; Hassall bodies were not present.

The liver capillaries were wide and the liver cells small, containing many fat drops. The portal spaces were in some regions large and rich in cells with shorter or longer offsets without forming pseudoacini. In addition to fibroblasts there were cells with a pale oval or indented nucleus and some lymphocytes and plasma cells. The gall ducts had not increased in size.

In the stomach and bowels serious postmortem changes made the study of finer cell structure impossible. One could be sure that no important proliferation of cells was present. The other internal organs showed nothing significant on microscopic examination.

While the biopsies of the "cysts" situated in the scapula gave the typical structure of an eosinophilic granuloma, the internal organs gave quite another picture. In the lungs there were important changes; they were found to be rich in foam cells without eosinophiles, giving the picture of a lipid granulomatosis. The lymph nodes in the mediastinum and the mesentery exhibited a focus-like proliferation of reticulum cells, while the spleen presented a diffuse increase of reticulum cells. In the lungs heavy fibrous changes were seen in the granulomata. The thymus was fibrous. In the spleen and the lymph nodes no fibrosis was found. The changes in the liver were not specific enough for any deductions. The first two skin biopsies showed nothing significant; the third gave the picture of a malignant reticuloendotheliosis. This patient had combined lipid granulomatosis of a normocholesteremic nature with the acute infective reticuloendotheliosis of Letterer-Siwe disease and an eosinophilic granuloma of one bone.

Abt and Denenholz's study of the noninfectious forms of nonlipid reticuloendotheliosis led to the construction of the Letterer-Siwe syndrome consisting of the following: hemorrhagic diathesis, swollen nodes all over the body, anemia, fever, hepatomegaly, splenomegaly, and bone affections. It has a bad prognosis and is nonhereditary in character, with an unknown origin. The most characteristic fact is that this is a system disease. Apparently the Hand-Schüller-Christian syndrome is more or less limited to the bones, giving the picture of skull defects, exophthalmos, polydipsia, and dermatological symptoms, but Rowland demonstrated that, histologically, reticulum cells, histiocytes, and foam cells laden with cholesterol with elements of acute inflammation are the most significant findings.

Eosinophilic granuloma has been studied since 1940 (Otani, Ehrlich, Jaffe, Lichtenstein) as a bone disease, while the skin form was already known earlier. We know that eosinophilic granuloma of the bones may be present as a solitary as well as a multiple affection with a rather favorable prognosis after conservative surgical therapy. Of the patients in 86 cases gathered from medical literature (Hadders 1948), 60 showed a solitary and 26 a multiple site. It is not astonishing that connections between the Hand-Schüller-Christian syndrome and eosinophilic granuloma are made from the beginning on and that these two affections may be related to the acute malignant infective reticuloendotheliosis. If Deelman and others are right in supposing that the "ur" reticulum cell retains the capability of metaplastic development—for instance, into foam cells or mother cells of the lymphocyte—we may consider these three affections as having one base.

Some years ago I studied two cases of acute malignant reticuloendotheliosis which give support to this hypothesis.

A. H., a girl aged 4 years, the second child of a healthy father and a mother suffering from tuberculosis, complained for some weeks of bone ache followed by blue-red skin infiltrations at the right thigh, right forearm, and right hip, with fever and swollen nodes in the axillae, the groins, and the neck. Biopsy of a node showed the picture of malignant reticulosis with disappearance of the node structure; the proliferating cells developed into lymphoblasts. Biopsy of the skin showed enormous proliferation of reticulum cells with slight leukemic character. The x-ray examination failed to show bone focus. Marrow biopsy (de Vries) proved the acute infective reticuloendotheliosis, but the second one two months later gave the picture of lymphatic

leukemia. The child died after an illness of four and one-half months with purpura, hepatomegaly, splenomegaly, and swollen nodes; clinically, she was a victim of acute lymphoblastic leukemia. The postmortem examination (Professor Deelman) confirmed the diagnosis of Letterer-Siwe disease progressed into acute lymphatic leukemia.

In this case the difference between the first biopsies and the following stage of the disease was so striking that we doubted our diagnosis.

T. V., a boy, the second child of healthy parents, fell ill with enormously swollen nodes in the neck, giving the appearance of acute pseudoleukemia. In the mother's family there existed a distinct hereditary trait to die of cervical carcinoma; the mother had visited a gynecologist for a cervical biopsy; findings were negative. Along with having swollen nodes, our patient presented a picture of anemia, purpura, hepatomegaly, splenomegaly, pressure on the bronchi by swollen mediastinal nodes, and leucocytosis. The biopsy of a node gave the picture of acute malignant reticuloendotheliosis with giant cells resembling Langhans cells (Professor Deelman). We tried to prevent death by suffocation by x-ray treatment of the mediastinal nodes. The child died after an illness of four weeks from anemia and extreme leucopenia. Postmortem examination (Professor Deelman) presented the picture of a systemic malignant reticulosis in which the reticulum cells did not mature to a known cell type. Instead, the cells were so swollen that Professor Deelman thought there was a beginning storage of unknown material in these large protoplasma masses.

According to Hadders the histiocytic reticulum cell may show metaplasia into (*a*) foam cells, as in cases of lipid granulomatosis; (*b*) fibroblasts, or fibrocytes; (*c*) giant cells, or macrophages, or (*d*) lymphoblasts.

The eosinophilic granuloma perhaps may not be a real disease but only a phase in a very complicated metabolic and reticuloendothelial process.

When we look over our own very interesting case in which we saw combined the lipid granulomatosis with malignant reticuloendotheliosis and eosinophilic granuloma we incline to look at the skin as the first site of a metabolic defect. It is without any doubt that the so-called "eczema" existed already in the second month, giving the aspect of a xanthomatosis of the skin three months later. This aspect changed, but we know that real xanthomatosis may disappear from the skin.

A healthy baby girl was born with a curious affection of the skin of the back. It was a typical case of xanthomatosis of the skin which disappeared after some months. The baby, who developed quite well, suffered at the age of 6 months of "petit mal with Salaam tics." Findings on electroencephalogram and ventriculography proved that the left hemisphere was deformed, and waves and spikes were found. Since the father and mother were cousins, there was no cerebral dysrhythmia. From the neurological side the connection between the skin affection and the cerebral dysrhythmia had been supported.

SUMMARY

Clinical and postmortem study is given of a girl aged 17 months who suffered from malignant reticuloendotheliosis with normocholesteremic lipid granulomatosis and eosinophilic granuloma in which treatment with antibiotics, corticotropin (ACTH), and x-ray did not change the malignant prognosis. The child died by orthopnea, severe cyanosis, and hypertrophy of the right heart because of the lungs losing the alveolar structure.

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MECONIUM ILEUS, MECONIUM PERITONITIS, AND VOLVULUS OF ILEUM WITH CYSTIC FIBROSIS OF PANCREAS

Report of Two Cases with Review

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CYSTIC fibrosis of the pancreas has been the subject of extensive investigation and speculation during the last 15 years. The disease may be manifest at birth, associated with meconium ileus or meconium peritonitis. More commonly, however, the pancreatic achylia and respiratory-tract infections typical of this disease occur during the first year of life, and it is this stage that is generally recognized. During early childhood, cystic fibrosis of the pancreas may produce symptoms not unlike those observed in the celiac syndrome. The type of clinical disease is determined by the period of life during which the pancreatic achylia occurs.

REVIEW

Meconium ileus is partial or complete intestinal obstruction in the newborn infant due to inability to pass meconium as a result of deficiency of pancreatic enzyme associated with cystic fibrosis of the pancreas. The failure of pancreatic enzyme to reach the small intestine in sufficient quantities to dilute adequately and to digest the fats and proteins in the meconium results in the formation of thick tenacious putty-like material. Landsteiner [1] reported the first case associated with fibrocystic disease of the pancreas, and about 65 cases have been since recorded.[2] Farber [3] reported 18 cases of meconium ileus due to cystic fibrosis of the pancreas. He showed by in vitro experiments that when the abnormal meconium is placed in contact with saline solution of pancreatin (1 to 10% at 37.5 C.) it is reduced to a liquid or semiliquid state. No mention was made of volvulus or meconium peritonitis in this series. Hiatt and Wilson [4] reviewed the literature and found 18 previously reported cases showing the association of cystic fibrosis of the pancreas and meconium ileus and added 8 of their own which were treated surgically. Five patients survived, the longest survival being 26 months. Montgomery [5] reported a case of meconium ileus in which the patient was alive and well more than one year after operation. A perforation of the ileum was described, but there was apparently no peritonitis or volvulus. Zuelzer [6] reported five newborn patients with meconium ileus and cystic fibrosis. Each was surgically explored. No mention was made of volvulus. One case presented multiple adhesions suggesting previous fetal peritonitis. All died shortly after operation. Autopsy disclosed no gross abnormality of the pancreas. The microscopic changes were typical of cystic fibrosis. Surgical therapy has been mostly discouraging, as the fundamental disorder of the pancreas persists despite removal of the meconium.

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Meconium peritonitis results from extrusion of sterile meconium into the peritoneal cavity through a perforation in the intestine before, during, or immediately after birth and may be caused by traumatic rupture of the intestine during labor and delivery, intestinal atresia, intussusception, or volvulus. Approximately 100 cases of meconium peritonitis have been reported,[7] and some have been associated with meconium ileus. The peritonitis is a chemical or foreign-body type inflammatory reaction. The perforation is not usually detected, presumably due to healing. Calcium deposition may occur in the inflammatory reaction and may be visible on abdominal roentgenograms. Bruwer and Hodgson [2] found reference to 11 instances of fetal peritonitis with focal calcification, and this was visible on the roentgenograms in 5 cases.

Volvulus of the ileum or midintestine associated with meconium ileus was present in 5 of the 18 cases reviewed by Hiatt and Wilson [4] and occurred in 5 of the 8 cases they presented. The two cases presented by Bruwer and Hodgson [2] also had volvulus of the small intestine, as did our two cases. Volvulus has thus occurred in 14 of 30 selected cases. The volvulus may be related to the vigorous peristaltic action required to propel the mucilagenous meconium or to the size and weight of a hypertrophied and elongated loop of small intestine frequently noted in meconium ileus. This localized segmental hypertrophy has suggested the possibility of a neurogenic abnormality such as occurs in Hirschsprung's disease as an etiologic factor in meconium ileus.[2] Absence of myenteric plexuses has been described in some cases.[8]

We have recently observed two male siblings who had cystic fibrosis of the pancreas associated with meconium ileus, meconium peritonitis, and volvulus of the midileum. One was treated surgically, the other was not. These cases are presented, concepts of etiology and pathogenesis are reviewed, and aids in diagnosis and methods of therapy are summarized. It is of interest that this mother gave birth to a third child (female) at this hospital April 5, 1953, and at present there is no indication of cystic fibrosis of the pancreas in this sibling.

REPORT OF CASES

Case 1.—B. K., a premature white baby boy, was delivered April 13, 1951, of a 24-year-old primigravida mother after 34 weeks gestation. There was no history of the mother indicating serious illness, operations, or injuries. There was prepartal care from the second month of pregnancy, and there had been no bleeding, albuminuria, hypertension, or other abnormal signs or symptoms. Pelvic measurements were normal. The father and mother were Rh positive. The mother felt no fetal movements for four days, from April 4 to April 8. Fetal heart sounds were not heard on April 7, but were detected on April 10. X-ray pelvimetry revealed normal adequate measurements and no evidence of fetal death. No calcification was observed in the fetal abdominal cavity. Labor was of less than 12 hours' duration, and the child was delivered from a right occiput anterior position. At birth the baby was found to have a greatly distended abdomen. No external congenital anomalies were noted. The attending physician noted that the mother had polyhydramnios.

The condition of the infant was poor from the time of birth. There was cyanosis, and the respirations were weak and shallow. The abdomen was extremely distended and mottled over the lower portion of the anterior wall. Oxygen was administered, but the patient did not respond. Death occurred nine hours after birth. Abdominal roentgenograms were not obtained.

Autopsy (1028) disclosed a fairly well-developed and well-nourished white baby boy weighing 2,210 gm. There was moderate cyanosis, and the abdomen was markedly protuberant. The circumference of the head was 29 cm.; of the thorax, 29 cm., and of the abdomen, 33 cm. The viscera of the abdominal cavity were displaced by a large, well-defined, friable, dark-brown, green, and grayish-brown mass of exudate, hemorrhage, and meconium which occupied the

anterior and lateral portions of the midperitoneal cavity and which had an estimated volume of 200 cc. The margins of this zone were composed of a thick layer of friable, purplish-red, and mottled-yellow material and tissue which was closely adherent to the serosal surfaces of the ileum, jejunum, and colon. The mesentery and peritoneum, except for this well-localized peritonitis, were smooth and glistening.

The small intestine was tortuous, and many loops were entwined about and adherent to one another by exudate in the region of the peritonitis. A 360-degree volvulus, involving a loop of ileum 10 cm. long, was present, and this loop was purplish-black, friable, and necrotic. The surfaces, in part, were adherent to adjacent loops of ileum. A perforation or site of rupture was not detected, although it is to be noted that the tissues were friable, easily torn, and covered with exudate, and, despite care, a minute site of rupture may have been missed. Upon dissection of the small intestine, the focal point of the volvulus was considered to be approximately equidistant between the ligament of Treitz and the ileocecal valve. A Meckel's diverticulum was not identified. Proximal to the volvulus, the small intestine was slightly distended and hypertrophied and contained thick green inspissated material. Distal to this site, the lumen was collapsed, and no gross meconium was visible. The entire large intestine was collapsed, averaged 0.6 to 1.0 cm. in diameter, and contained small amounts of gray mucus. No meconium was present. The appendix was situated in the right lower quadrant and not remarkable. Grossly, the pancreas was not remarkable and was of average size. The extrahepatic bile ducts were not remarkable.

Microscopic studies of the pancreas disclosed slight to moderate cystic fibrosis. The lumens of many of the acini and small ducts were dilated and contained homogeneous pink-staining material. There was significant increase in interstitial fibrous connective tissue. The serosa of the portions of the small and large intestine which walled off the peritonitis disclosed organizing and recent inflammation, hemorrhage, necrosis, focal calcification, and foreign-body material (meconium). The reaction was typical of meconium peritonitis. The site of perforation was not detected. The loop of ileum which was involved in the volvulus was necrotic and hyperemic.

The lungs were the seat of marked atelectasis neonatorum with many squamous cells present in the alveoli. The other viscera were not remarkable.

Case 2.—B. K., a white baby boy, was born at term on March 23, 1952, weighing 2,500 gm. The pregnancy was uneventful. Labor was of 36 hours' duration and difficult. Because of marked abdominal distention of the infant, the obstetrician punctured the abdomen in two places in the left lower quadrant with the release of pale-yellow thin fluid. Delivery was then accomplished by podalic version extraction. The infant was noted to be cyanotic, and there was marked abdominal distention. The rectum was empty, and no meconium was passed. Abdominal roentgenograms were not obtained. No mention was made of hydramnios.

The infant was given penicillin and Ringer's solution. Twelve hours after delivery, during which time no urine or meconium was passed, the abdomen was opened through a vertical midline incision. Exploration revealed moderate to marked amounts of soft, friable, partially necrotic, grayish-green mottled red and brown material in the region of the left upper quadrant. The patient had a 180-degree volvulus of a loop of midileum. The mesentery was markedly constricted in this region. There was no gangrene. The volvulus was manually reduced. Distal to the volvulus, the ileum and the ascending and transverse colon were small and were filled with inspissated putty-like meconium. The descending colon contained thick gray mucus. The splenic flexure of the colon was the site of a rent (probably surgical artifact) through which the abnormal meconium was removed and the proximal and distal bowel irrigated with saline. A catheter was threaded through the rent in the splenic flexure into the proximal colon and brought out as a loop colostomy in the upper abdomen. The abdomen was closed without drainage.

Throughout the postoperative course, saline infusions were given through the colostomy. Pancreatin solution was not used. Ringer's solution and penicillin were continued. Labored respirations, cyanosis, and pallor persisted. The baby did not have any stools but did void small amounts of urine shortly before death. Death occurred 24 hours following surgery.

Autopsy (1128) disclosed inspissated meconium in the terminal portion of the ileum and proximal colon. The midileum at the site of the previously reduced volvulus averaged 2 cm. in diameter. Distally, the ileum averaged 1 cm. in diameter. The colon varied between 0.6 and 1 cm. in diameter. The pancreas weighed 5 gm. and measured 7.0 cm. by 1.2 cm. by 0.8 cm. in

greatest dimensions. The head and body of the pancreas were covered, in part, by a thin layer of greenish-gray mottled red and brown exudate. Multiple transections of the pancreas revealed firm, lobulated, yellowish-white, and pink surfaces. The pancreatic ducts could not be identified in any portion of the pancreas to determine their gross patency. The tail of the pancreas was markedly distorted, mottled grayish-green, red, and brown, and was surrounded by a large amount of soft, friable, green-and-brown exudate which was bounded by the stomach and diaphragm superiorly, the spleen laterally, the transverse colon inferiorly, and the left lobe of the liver medially. There was no gross calcification. Cultures were not made. The extrahepatic biliary tract was patent throughout.

Microscopically, the head, body, and tail of the pancreas showed widespread focal replacement of parenchyma with dilated ducts and acini which formed cysts of varying size. Many of these cysts contained homogeneous and concentrically laminated acidophilic masses. These cysts were lined by a single layer of cuboidal or flattened epithelial cells. The changes were most marked in the tail of the pancreas. The islets of Langerhans were normal. The tail of the pancreas and the pericolic and perisplenic areas showed focal organizing hemorrhage with inflammation. Focal calcification was not observed. The other viscera were not remarkable, and there were no congenital anomalies present.

COMMENT

These two cases are of interest because they call attention to the occurrence of a triad of conditions in the neonatal period which are related to cystic fibrosis of the pancreas. Meconium ileus, although uncommon, is in general the best known. Meconium peritonitis has been described only infrequently and is seldom considered in differential diagnosis. Practically no attention has been given to volvulus of the ileum, despite its frequent occurrence with meconium ileus. This triad should be considered in the differential diagnosis of all instances of abdominal distention occurring in the newborn associated with failure to pass meconium per rectum that are not clearly due to anomaly of the rectum or anus, such as imperforate anus. The presence of volvulus in the newborn should arouse suspicion of the possibility of associated meconium ileus and cystic fibrosis of the pancreas.

Intestinal obstruction due to abnormal meconium occurs with varying degrees of severity. In those cases due solely to volvulus, adhesive band, or intestinal atresia, relief of the mechanical obstruction will generally restore the flow of meconium. In neonatal cystic fibrosis of the pancreas, however, the pancreatic achylia is a fundamental factor, and the resultant obstruction is usually severe and requires surgical removal of the meconium or administration of pancreatin solution to alter the physical state of the inspissated meconium.

The pathogenesis of cystic fibrosis is not completely known. Studies [9] have indicated that the incidence among siblings approximates the 25% expected of a Mendelian recessive trait. Abbott and co-workers [10] reported 102 cases of cystic fibrosis representing 77 families of whom 14 (13.2%) showed more than one child afflicted. Eighty-one of the 102 cases were autopsied, and 10 deaths were attributed to meconium ileus. Avitaminosis A is probably the result of inadequate absorption from the intestinal tract rather than a cause. Infection and the Rh factor have been hypothesized as etiologic agents but have not been proved. Norris and Tyson [11] looked upon cystic fibrosis as a dysontogenetic phenomena, like polycystic kidney and liver, the result of delayed resorption of primitive tubules. Baggenstoss and co-workers [12] studied five cases of cystic fibrosis of the pancreas and suggested that congenital atresia of the pancreatic ducts resulting from an embryologic malformation may be the cause. They no longer held to their previously reported concept of a deficiency

of secretin in the small intestine to be the primary factor. Farber's [13] earlier studies showed that congenital atresia or stenosis of the pancreatic ducts did not occur in the majority of their series of 87 postmortem cases. He observed marked alteration in the composition of the secretions of other glandular structures such as intestinal glands, bronchial glands, and salivary glands and presented the concept of a systemic mucus glandular disturbance as being a fundamental factor in this disease. These changes, however, are rarely observed in the neonatal stage of the disease. Andersen [14] has considered the widespread changes in mucous glands to be the result of nutritional disturbances rather than to be due to generalized congenital disease.

DIAGNOSIS

The preoperative diagnosis of meconium ileus usually cannot be made with certainty. The presence of a distended abdomen and the failure of passage of meconium should arouse suspicion. Abdominal roentgenograms may show dilated loops of small intestine in which fluid levels may be visible. In addition there may be many minute gas shadows in shadows of uniform solid density distal to the fluid levels.[2] This is considered to be due to a mixture of gas and tenacious meconium. This was described by Neuhauser [15] and may occur in imperforate anus.[2] Focal calcification of the peritoneal cavity may occur, and this is highly suggestive of meconium peritonitis. The presence of free air in the peritoneal cavity indicates rupture of the gastrointestinal tract and should arouse suspicion of meconium peritonitis or volvulus with perforation. The diagnosis should be strongly suspected if a sibling had previously died of proved or suspected meconium ileus. The absence of trypsin and lipase in duodenal-pancreatic enzymes is of great aid in diagnosis. The gelatin-film test also may be used to demonstrate the absence or diminution of trypsin in samples of meconium.

TREATMENT

Early surgical intervention is only temporarily helpful in meconium ileus, although a few patients have survived.* Surgical treatment is directed toward complete removal of the abnormal meconium as quickly as possible. This is accomplished by a process of manually "milking out" the inspissated meconium through an enterostomy performed in the most distal segment of dilated ileum. Following complete removal of the mucilagenous meconium, the proximal and distal intestine is irrigated with normal saline solution mixed with 5% pancreatin solution. Some surgeons prefer to close the enterostomy rather than perform an ileostomy or colostomy. Volvulus of the ileum may be present, and this should be treated by manual reduction if viable or by resection if gangrenous. The abdomen is closed without drainage. Splanchnicectomy was performed by Ayers and co-workers [16] in 24 cases of cystic fibrosis of the pancreas with notable benefit in only three cases. This has not been reported in the neonatal stage. Meconium peritonitis due to atresia of the terminal ileum has been treated by excision of the involved area, with subsequent healing and gradual disappearance of peritoneal calcification.[7] This case, however, was not one of cystic fibrosis of the pancreas. Medical management includes a low-fat-high-protein diet, vitamins, oral pancreatin, and administration of antibiotics for intercurrent infections.

* References 4 and 5.

SUMMARY

Attention is called to a triad of conditions, namely, meconium ileus, meconium peritonitis, and volvulus of the ileum, which may be associated with cystic fibrosis of the pancreas in the neonatal period.

Two cases in which this triad of conditions were present in consecutive newborn male siblings are reported. One was treated surgically and died 24 hours after operation. The other died nine hours after birth.

Meconium ileus, meconium peritonitis, and volvulus of the ileum should be considered in the differential diagnosis of all instances of abdominal distention occurring in the newborn associated with failure to pass meconium per rectum that are not clearly due to anomaly of the rectum or anus.

Cystic fibrosis of the pancreas is the underlying cause of the abnormality of the meconium. The pancreatic achylia results in failure of normal digestion of meconium. The cause of cystic fibrosis of the pancreas is unknown.

Concepts of etiology and pathogenesis, aids in diagnosis, and methods of therapy are presented. Previously reported instances are reviewed briefly.

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Progress in Pediatrics

TREATMENT OF ACUTE PHASE OF POLIOMYELITIS

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IN THE absence of any specific remedy, the medical care of poliomyelitis patients requires (*a*) an understanding of the natural history of the primary disease with its numerous secondary complications and (*b*) a discriminating clinical capacity to individualize each whole patient so that the best available symptomatic management and anticipatory guidance is provided. In the acute-stage care of complicated cases, physicians representing several unrelated medical and surgical specialties are involved. Under such conditions it is essential that one physician, be he family doctor, internist, or pediatrician, take the helm and assume over-all clinical responsibility. This simple point is often overlooked, resulting in anxiety and confusion concerning the immediate prognosis and the ultimate outlook for restitution to a normal life.

For convenience, the management is discussed according to the clinical form of poliomyelitis, i. e., abortive, nonparalytic, and paralytic. It must be clearly understood that one form may evolve into a more severe form, as pointed out in Dr. Grulee's section of this symposium dealing with diagnosis.[1] For the most part, the comments which ensue relate to the first two weeks of acute illness.

ABORTIVE POLIOMYELITIS

Although impossible to establish definitively, the presumptive clinical diagnosis of abortive poliomyelitis is frequently applicable during epidemics. Rather than subject such patients to hospitalization, it is preferable to treat them at home expectantly, thereby avoiding fear, fatigue, and undue manipulations. Injections are probably best avoided. It is believed that once the symptoms of abortive poliomyelitis appear, the injection of gamma globulin has no effect.[2] Simple analgesics, mild sedatives, an agreeable diet, and bed rest until the patient has been fever-free for several days are adequate. Constipation is not infrequent and may require attention. Overexertion should be avoided for the ensuing two weeks. All such patients should be closely examined approximately two months after onset to be certain that minor grades of neuromuscular involvement cannot be detected.

NONPARALYTIC POLIOMYELITIS

Treatment at home is feasible and advantageous, particularly in urban practice. The therapy noted above must be supplemented because of the discomfort frequently engendered by muscle spasm and tightness of the neck, back, and extremities. For

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this purpose the application of moist heat in the form of wrung-out woolen packs can be improvised. An infrared lamp, while less effective in relieving spasm, is simple and brings considerable comfort. A firm bed is desirable and is improvised by placing a board, door, or table leaf beneath the mattress. Bladder retention may occur, and its management is described below in connection with paralytic patients. The degree and duration of muscle spasm and tightness is variable, but may go on for weeks, requiring hot packs and gentle physical therapy. The patient should be examined preferably by a physiatrist or orthopedist a month after apparent recovery for minor residual neuromuscular defects. Minor muscular defects, if unrecognized, may result in significant posture problems or deformities of the feet and spine at a later date, particularly in growing children.

PARALYTIC POLIOMYELITIS

Patients with mild degrees of peripheral paralysis may be treated at home, particularly in urban practice. Lengthy arduous journeys in the early acute stages may aggravate the severity of ensuing paralysis. The psychological advantages to the patient are considerable if appropriate follow-up care in the office or outpatient department is arranged and suitable measures taken during the acute stage to prevent skeletal deformities. Individual judgment is required regarding the necessity for immediate hospitalization in any given instance with mild paralysis. Because of the threat of extending paralysis, rural patients must usually be admitted to a hospital as soon as any paralysis has been detected. The essential thing is to insure continuity of long-term care, a feature which does not necessarily follow simply because a patient has been hospitalized in the acute stage of illness.

HOSPITAL CARE

General Considerations.—Protracted expert hospital care is essential for achieving the best results for extensively paralyzed patients and is mandatory for those who have impending respiratory embarrassment with or without bulbar or encephalitic symptoms. The diversity of professional skills required to produce best results in this group of patients is such that it is desirable to have such patients in general rather than special hospitals during the acute stage. There should be available in each such hospital one or more senior nurses who have received special instruction in the care of poliomyelitis patients.* One physician must assume clinical responsibility for the patient despite the need for several specialty services. Prognosis is an integral part of management, and its pronouncement is his job. The assistance of clergymen is often invaluable, and their usefulness exceeds merely officiating at the time of the impending death of the patient.

General Principles Applicable to Paralytic Hospitalized Patients.—1. A display of quiet confidence on the part of all staff members is essential. Wide latitude in permitting visiting on the part of the family is helpful for both patient and family. Many parents are able to do a great deal toward the comfort, care, and feeding of their own children.

* The state representatives of The National Foundation for Infantile Paralysis have lists of courses prepared for physicians, nurses, and others, and may be of assistance in developing *ad hoc* courses.

2. It is desirable to avoid repetitious examination and unnecessary handling, especially during the painful days of early illness.

3. The maintenance of suitable body alignment is desirable in order to prevent subsequent deformities; sandbags and blanket rolls may be used to achieve alignment. Boards beneath and a footboard 4 to 6 in. (10.2 to 15.2 cm.) beyond the mattress are very desirable. Small children cannot always be persuaded to keep their feet at the desired right angle against the footboard; in such cases the wearing of their own shoes may be helpful.

4. Opiates and other depressant drugs must be avoided in the face of extending paralysis, particularly shoulder-girdle involvement of the type which may precede actual respiratory dysfunction. Once the ventilatory status is secure, barbiturate sedation may be used.

5. Constipation is common, and the danger of fecal impactions must be anticipated. Small-volume glycerine-and-water enemas or glycerine suppositories are more effective than oral laxatives in the first week or 10 days of illness.

6. Transient bladder paralysis occurs in 15 to 25% of patients.[3] A trial with the parasympathomimetic drug furtrethonium (Furmethide) 5 to 10 mg. orally or 2.5 to 5.0 mg. hypodermically, may induce voiding in 10 to 30 minutes; it is ineffective in some patients and may cause nausea, vomiting, or palpitation in others. Aseptic intermittent catheterization is preferred to indwelling catheterization in this short-lived complication. A soluble sulfonamide in full therapeutic dosage should be given until several days after the final catheterization and the urine sediment examined microscopically.

7. Pharmacologic substitutes for the muscle-relaxing effects of moist heat are generally not efficacious. Experience with drugs proposed for this purpose, namely, thiamine, nicotinic acid, neostigmine, intravenous procaine, mephenesin, quinine, curare, and benzazoline (Priscoline) has been generally unrewarding. Benzazoline induces flushing, which brings comfort to some patients; curare, while effective, is rather risky. The application of hot packs can be taught to auxiliary personnel and need not be done by nurses or physical therapists alone.

8. Although sensory disturbances do not occur in poliomyelitis, constant vigilance is required if pressure sores are to be avoided.

9. Unless there is actual vomiting, an appealing light diet and a full fluid intake should be encouraged from the beginning. Anorexia is a common problem of the first few days and if unchecked initiates a protracted vicious circle. Mothers are encouraged to bring the child's favorite foods and to do the feeding initially. Small frequent meals are preferred. An indwelling polyethylene gastric tube is often necessary to insure adequacy of caloric and fluid intake. Severe nutritional failure in convalescence is often attributable to undue delay in early feeding.

10. All staff members should be alerted to report at once any change in rate, depth, or rhythm of respiration and any change in voice, such as nasal twang or speech characterized by short jerky sentences.

MANAGEMENT OF BULBAR AND RESPIRATORY POLIOMYELITIS

Deaths from poliomyelitis during the acute stage are largely confined to patients with bulbar and respiratory paralyses. There are three principal forms.

I. Bulbar Poliomyelitis.—In cases classified as bulbar, the motor cranial nerve nuclei are involved; particular danger is associated with involvement of the 9th, 10th, and 12th cranial nerves. Also involved may be the "vital centers" of the brain stem, which regulate respiratory and cardiovascular dynamics. The chief problem in the course of treatment is the regular removal of secretions from the paralyzed pharynx and avoidance of their aspiration into the lungs. The head low prone position with the face turned to one side favors the drainage and removal of secretions. Patients with bulbar poliomyelitis without arm involvement are frequently willing and able to aspirate their accumulated secretions with a mechanical aspirator equipped with a rigid or semirigid tip. Tracheotomy (below) is occasionally necessary, even in this group with "pure" bulbar disease, if the airway cannot be kept clear. This is particularly so if the muscles of the larynx, tongue, or jaws are also severely involved.

An occasional bulbar patient develops sufficient central dysrhythmia of breathing to produce hypoxia and hypercapnia. For this small group and under other special circumstances, the electrophrenic respirator [4] may be useful.

II. Spinal Paralytic Poliomyelitis with Respiratory Insufficiency.—Respiratory insufficiency complicating "pure" spinal poliomyelitis reflects involvement of the respiratory mechanism per se. The direct and usually effective remedy is mechanical artificial respiration. With very mild insufficiency, the aid of a rocking bed or of a cuirass-type respirator may suffice. The selection and use of respirators is considered below.

III. Bulbospinal Poliomyelitis with Respiratory Insufficiency.—Unfortunately, "pure" bulbar and "pure" spinal poliomyelitis are less common than the mixed form. The therapeutic aim in these cases is to provide artificial respiration, to maintain an adequate airway, and to anticipate and thwart certain additional complications (below). If lives are to be saved in the critical early days of illness, the physician in charge must be able to call upon a skilled anesthetist and a laryngologist or thoracic surgeon. The importance of nurses who have received instruction in the handling of such patients cannot be overemphasized.

Use of Mechanical Respiratory Aids: Tank respirators. The tank respirator provides the maximum artificial ventilation for the patient. Cuirass respirators and rocking beds are less efficient but may suffice for mild degrees of ventilation failure in the acute stage and are very valuable in the process of weaning patients out of the tank respirator in convalescence. In the early stages, a common failing may be paraphrased as "too little pressure too late applied." A smoothly planned stage setting is essential if the patient is to adjust to the machine; time should be taken to explain to the patient the purpose and method of operation of the machine. It is vital to conceal any sense of haste and anxiety which may understandably exist. The presence of a well-rehearsed and reassured parent often makes possible the smooth transfer and synchronization to the machine of a terrified child. Provided the major airway is cleared or assured through tracheotomy, the use of barbiturate sedation may assist the patient in "letting the machine take over."

Suggested initial trial pressure and rate settings are indicated in Table 1. Such initial pressures and rates must be adjusted until clinical evidence of improvement is noted by (1) improvement of general appearance with disappearance of restless-

ness, pallor, or cyanosis; (2) adjustment to the rhythm of the respirator, with cessation of extra efforts by the accessory muscles of respiration; (3) relaxed appearance, dozing, or sleep.

When the adjustment of pressure and rate results in inadequate ventilation one may clinically note that (1) the patient attempts to take extra little breaths between phases of the machine, (2) anterior movements of the chin and flaring of the alae nasi appear, and (3) pallor, anxiety, restlessness, and, ultimately, cyanosis reappear.

During the early febrile days with respiratory insufficiency it is better to overventilate when in doubt. The negative pressure of the tank respirator required to produce normal tidal volume in acute poliomyelitis is much greater than the usual intrapleural pressures required for the same amount of ventilation of normal lungs. This change in "distensibility" of the lungs occurs early in illness.[5] Tracheotomy tubes (below) introduce additional resistance to the inflow of air and may make it necessary to use higher tank pressures than anticipated.

There is no definite formula which can be given for determining the respirator pressure values to be used. Ventilation must be adequate to maintain normal levels of carbon dioxide and oxygen in the arterial blood; the pressure required to do

TABLE 1.—*Suggested Initial Trial Respirator Pressures and Rates**

Age, Yr.	Pressure, Cm. H_2O	Rate/Min.
2	−14	32†
2-10	−16	24
10-15	−16	20
15	−18	18

* Frequent adjustments based on clinical response and tidal air measurements are necessary in the beginning. Alteration in amplitude is generally more helpful than adjusting the rate.
† Infant respirators only are designed to operate this rapidly.

this can vary widely within a short period of time in the same patient. Blood gas determinations are not yet generally feasible; oximeter readings give no indication of the amount of carbon dioxide retained in the blood. Thus respiratory acidosis due to inadequate exchange of carbon dioxide may exist even though blood oxygen levels are maintained through oxygen inhalation therapy.

The amount of air which such patients need should be measured when possible, rather than judged empirically. For patients over the age of 5 years, it is generally possible to do this either by mask or with an adapter in patients with tracheotomy. We have used, with satisfaction, the Bennett Ventilation Meter.† Recording spirometers or basal metabolism machines are satisfactory. Table 2 gives a range for the amount of tidal air which should be displaced with each cycle during the early phase of illness. A tentative rate of the machine is also given. The figures mentioned as *initial trial* settings of the respirator (Table 1) may be inadequate to displace this amount of air. Both positive and negative pressure can be used together with cumulative net effect. Indeed, if one utilizes only negative pressure, it may be necessary at times to employ —25 cm. of water or more, at which time nursing procedures are difficult, as it is almost impossible to maintain a tight seal. In

† Obtainable from J. J. Monaghan Company, 500 Alcott St., Denver.

patients who have hypotension and appear to have impaired cardiac filling, it is indeed much more desirable to use "atmospheric pressure," for example, —10 and +10 cm. in each cycle, yielding a total effective pressure of 20 cm.

Vital-capacity measurement is an even better index of when patients require respiratory assistance and how they are progressing, but it generally requires more cooperation from the patient than the mere measurement of tidal air. It is particularly in the convalescent respirator patients that vital-capacity measurements are most useful in determining progress, fatigue, etc.

Placement of a patient in a respirator introduces a series of responsibilities, including that of ultimately getting the patient out of the machine again. Weaning, although beyond the scope of this paper on acute care, should begin on the first day. The respirator should be opened from time to time, even if only for a few seconds, and at the time that this is done the patient should be given continuous verbal reassurance. Simple achievement charts can be improvised to graph the seconds, minutes, or hours per day during which the machine has been kept open. Chronic dependency on a respirator is easier to prevent than to treat.

TABLE 2.—*Tentative Tidal Air Volumes Desired During the Acute Febrile Stage* *

Yr.	Cc./Cycle	Rate/Min.	Yr.	Cc./Cycle	Rate/Min.
<2	100-150	30-32	10	300-400	22-24
3	150-200	24-28	11	300-400	20-22
4	200-250	24-26	12	400-500	20-22
5	250-300	24-26	13	450-550	20-22
†			14	450-550	20-22
6	250-350	24			
7	275-375	24	Adults		
8	275-375	24	Female	450-550	18-20
9	350-400	22-24	Male	500-600	18-20

* The pressure settings needed to provide this amount of air displacement may vary greatly in the same patient from time to time. These measurements, while useful, must be coupled with clinical response. When uncertain, it is better to overventilate, at least for the first few days.

† Under 5 years of age, it is difficult to measure accurately the amount of air being displaced.

Tank respirators become very hot and uncomfortable if the lights therein remain on. A pan of solid carbon dioxide (dry ice) or a small insert fan blowing on a pan of ice in the tank has a cooling effect.

Cuirass respirators. Cuirass respirators enclosing the thorax and/or abdomen may be a life-saving device, as when the patient is being transported to the hospital. As ventilating machines they are less efficient than tank respirators. They may be useful when a tracheotomy is done before the patient is moved to a tank respirator. They may be used as the primary respirator if the degree of respiratory insufficiency is slight or for the patient who has an unmanageable terror of the tank respirator. It is not always easy to achieve and maintain a good fit to the body contour. The cuirass respirators have particular merit in weaning patients from the tank respirator.

Oscillating beds. The effect of a rocking bed is to produce passive inspiration as a result of the descent of the abdominal organs; during the head-down phase these viscera push the diaphragm upward. The value of the rocking bed as a primary "respirator" is limited to patients with minor degrees of respiratory insufficiency. It is extremely useful in weaning patients from the tank respirator.

Tracheotomy. "There is always that kind of feeling connected with a surgical operation in acute diseases, which prevents its being proposed, assented to, or performed, unless under nearly desperate circumstances, and when all other means have failed. In the case before us, the operation is performed at a time when the situation of the patient is the worst possible for success; when the nervous system has been profoundly injured, and the lungs, even though no primary complication may have existed, have become extensively congested."‡

Although written 125 years ago with regard to tracheotomy for croup, that statement is currently applicable in bulbospinal poliomyelitis. I confess to having been among the many who were conservative in adopting such a point of view. In the case of patients with combined bulbospinal involvement exhibiting beginning ventilatory insufficiency, tracheotomy should be done promptly. The procedure should preferably be done with a bronchoscope in situ in the trachea. This not only assures the airway but makes possible the use of positive-pressure ventilation by attachment to the anesthetist's manual bag. The emergency "stab-and-search" method, while life-saving on occasion, should not become necessary. A high opening (second tracheal ring) is preferred. Several ingenious collar depressors are available for use with tank respirators, but even with these free access and care of the tracheotomy may be difficult. The largest sized tracheotomy tube possible should be inserted in order that air-flow resistance be reduced to a minimum. The standard tubes are often too long and may impinge upon the anterior tracheal wall and even jostle the carina. We frequently use tubes whose distal end has been cut off 2 cm. Aspiration must be performed swiftly, since the presence of the endotracheal suction catheter rapidly leads to hypoxia and hypercapnia.

The tracheotomized patient with bulbospinal poliomyelitis differs in one important respect from patients tracheotomized for acute airway obstructions. He is unable to cough. A common error is to remove tracheotomy tubes too early.

All patients with the bulbar, spinal-respiratory, and bulbospinal forms of poliomyelitis should receive therapeutic doses of a suitable antibiotic, penicillin in large doses being preferred initially. Endotracheal and nasopharyngeal cultures may give cause for changing to other antibacterial therapy in the ensuing days or weeks.

"Heroic Measures." This term is a relative one. The use of a mechanical respirator is perhaps still regarded as heroic by some, and a tracheotomy is thought of as extreme by others. Yet these measures used early and wisely have saved many lives. It appears probable that we have only scratched the surface with respect to possible devices for maintaining ventilation and circulation. Better knowledge of normal and abnormal respiratory and circulatory physiology and improved technology may lead to improved control of the gaseous environment of other patients with ventilation failure in addition to those with poliomyelitis.

What about measures that might currently be defined as "heroic"? Two appear worthy of mention, cardiac massage [7] and intra-arterial infusion.[8] Abrupt cardiac arrest occurs occasionally in poliomyelitis. An immediate emergency thoracotomy was performed in 12 instances during a local recent severe epidemic. No lives were saved. A 2-year-old boy was restored to normal consciousness for four and one-half days following this procedure, requiring two additional maneuvers of digital cardiac

‡ Stokes, W.: A Treatise on the Diagnosis and Treatment of Diseases of the Chest, Dublin, Hodges & Smith, 1837, p. 220.

massage in the interim before succumbing to an asphyxial episode. The next longest survival period was two and one-half days. Better methods for the instantaneous detection and correction of abrupt cardiac arrest and for artificially maintaining circulation by other means are needed.

Intra-arterial transfusion has been attempted as an emergency measure for abrupt complete peripheral circulatory collapse in surgical patients. Such a circulatory collapse is a relatively uncommon but mortal complication in poliomyelitis and is probably the result of involvement of vasoregulatory centers in the brain stem. In one such patient (a 20-month-old boy), it was possible within five minutes to pump Type O unmatched blood into the radial artery. Restoration of cardiac filling was followed by a return of the peripheral pulse, normal blood pressure, and a return of consciousness. The place for this emergency measure remains to be determined. Intravenous blood if pumped rapidly with a high head of pressure may be equally effective.[9] Promptness and immediate readiness of equipment is the essential thing.

The acutely and sevely ill poliomyelitis patient has usually had normal cardiovascular, respiratory, and renal function up to within a few days before death looms. The prognosis for ultimate functional recovery of each of these internal organ-systems is excellent, provided means can be found for tiding the patient over the acute stage of disease.

ANTICIPATION AND MANAGEMENT OF CERTAIN COMPLICATIONS

1. Bronchopulmonary.—These include increased collection of mucus, bronchial plugging, atelectasis, secondary respiratory infections (tracheitis, bronchitis, pneumonia), pulmonary edema, tracheal ulceration, and pneumothorax. Abrupt periods of cyanosis erroneously ascribed to "central episodes" often yield to prompt reestablishment of pulmonary oxygenation and carbon dioxide removal.

An almost constant concomitant in the early stages of the severe spinobulbar tracheotomized poliomyelitis patient is the accumulation of thick tenacious mucopurulent material. With patients unable to cough it does not take long before this is sufficient to impair the transfer of oxygen and carbon dioxide across the barrier of the alveolar walls. Adequate body hydration and humidification of room air or oxygen helps prevent thick secretions. Simple saline or, for special circumstances, solutions containing trypsin, antibiotics, and a vasoconstrictor[6] may be instilled into the trachea prior to mechanical aspiration. Although difficult to assess their value, we administer iodides orally to such patients.

Careful attention to tracheobronchial toilet requires the following measures: 1. Frequent swift thorough aspiration through the tracheotomy tube. Flexible catheters cut at a 45-degree angle and smoothed in a flame are useful; by turning the patient's head sharply to the left it is frequently possible to enter the right mainstem bronchus or vice versa. Broncholavaging solutions may be very helpful. 2. Intensive antibiotic therapy is essential. I commence with large doses of penicillin and am then guided in part by alterations noted in the tracheal culture. 3. Bronchoscopy is done when simple aspiration fails to relieve obstruction.

Devices to produce intermittent deep breaths and to artificially simulate cough can be useful in preventing atelectasis. The "suck-and-blow" pressure of a household vacuum cleaner can be attached to a porthole of the tank respirator for this purpose.

II. Gastrointestinal.—A. Hemorrhage: The appearance of unexplained tachycardia, pallor, or shock followed by melena indicates severe gastrointestinal hemorrhage, which is not rare in bulbospinal poliomyelitis. Vigorous blood replacement is often required. We have on occasion been obliged to give as much as 2,000 cc. to a 5-year-old child and more for adults. Lesser degrees of enteric bleeding occur, not requiring transfusion. Coffee-grounds vomitus occurs terminally with some frequency.

B. Acute Gastric Dilatation: This mysterious complication may arise during the acute stage and also in convalescence. It exaggerates markedly the degree of ventilatory difficulty and is most distressing. Constant gastric aspiration plus the application of an ice bag to the epigastrium will sometimes relieve this dramatic, and at times mortal, complication.

C. Perforation: Although superficial mucosal ulcerations are common in severe poliomyelitis, actual perforation is not common. When the abdominal muscles are paralyzed, they are unable to develop the reflex spasm which ordinarily accompanies peritonitis. We have seen at autopsy unrecognized perforation with peritonitis in a patient who was in unexplained unresponsive shock but who at no time exhibited abdominal tenderness or rigidity.

III. Acute Hypertensive Encephalopathy and Convulsions.—Premonitory symptoms of dimness of vision, increasing headache, and drowsiness associated with a climbing blood pressure are not infrequent and may be followed by convulsions. In patients presenting the above findings it is advisable, having assured their respiratory status mechanically, to provide anticonvulsive therapy in the form of barbiturates. Magnesium sulfate intramuscularly will sometimes reduce the blood pressure and abate the symptoms, although it is less effective in poliomyelitis than in the acute hypertensive encephalopathy of acute glomerulonephritis of children. Of the autonomic blockading agents employed, Arfonad § has been the most effective in controlling the acute hypertension of poliomyelitis.

Convulsions from any cause add to cerebral anoxia and are to be avoided. The other causes for convulsions during the acute stage of poliomyelitis are (1) "febrile" condition, (2) preexisting epilepsy, (3) anoxia and hypercapnia, (4) "encephalitic" poliomyelitis without respiratory failure.

In patients with a past history of convulsions or those developing the premonitory changes of acute hypertensive encephalopathy, it has been our practice to commence diphenylhydantoin sodium therapy, which takes several days for effectiveness; in the interim we rely upon barbiturate anticonvulsant therapy.

IV. Hyperpyrexia Syndrome.—Unless checked immediately, this syndrome may result in fatality. It probably arises from involvement of the thermoregulatory centers and bespeaks severe brain-stem involvement. Ice packed directly on the patient is more efficacious than wet cloth packs in patients whose temperature is over 106 F. Since temperature elevation per se increases the body oxygen requirement sharply, temperature control is very important in these patients. Is it possible that systemic hypothermia could be safely applied over a number of days in order to reduce the total oxygen requirement?

§ Hoffmann-LaRoche, Inc., Nutley, N. J.—The chemical name is *d*-3,4(1′,3′-dibenzyl-2′-keto-imidazolido)-1,2-trimethylene thiophanium *d*-camphor sulfonate.

V. Pregnancy.—In the absence of respiratory insufficiency the management of this complication is not overwhelming. In gravid patients requiring respirator treatment, it is generally necessary to employ pressure settings higher than the same patient will require following delivery. With acute respirator patients at or near term, it is best to entrust the patient's ventilation under inhalation anesthesia to an anesthetist, perform elective Caesarean section without any trial of labor, and treat the patient's respiratory needs postoperatively in the usual way. Although occasionally a normal well-ventilated baby and mother will be the product of labor in a tank respirator, the usual outcome is a high mortality rate for both mother and baby; the planned arrangement mentioned above is preferred.

VI. Cardiovascular.—Abrupt cardiac arrest and abrupt shock-like states have been alluded to under "heroic measures." Other complications include the following:

1. Cardiac arrhythmias: The origin of these is not always certain; the cardiac regulating centers of the brain stem may be disordered; myocarditis may occur. When tachycardia persists, I have employed semirapid digitalization but am unable to assess its real merit.

2. Hypertension and pulmonary edema: So-called "neurogenic" pulmonary edema is mediated on the basis of arterial hypertension, which is common in severe poliomyelitis patients. It has been rather difficult to control the hypertension of the poliomyelitis patient in the acute stage with either magnesium sulfate intramuscularly or autonomic blockading drugs. The use of antifoaming agents endotracheally in the presence of actual pulmonary edema is helpful; aerosolized ethyl alcohol and Dow-Corning Antifoam A spray may be used.

3. Pulmonary embolism: Although it has been observed occasionally at postmortem examination, we have not been able to establish a premortem diagnosis of pulmonary embolism. This complication is exceedingly rare considering the extent of immobility of the patients. It may be that the relative youth of patients reduces the frequency of this complication.

VII. Convalescent Medical Complications to Be Anticipated.—A. Malnutrition: This should be anticipated and fought vigorously from the very beginning. Thin polyethylene gastric tubes should be inserted within the first few days after onset in the severe bulborespiratory poliomyelitis patient. All too frequently anorexia breeds further anorexia with disastrous results. When food by mouth is offered, it is well to employ small amounts given frequently, since gastric distention is not well tolerated by the respirator patient.

B. Urinary Infection and Calculi: The rate of skeletal decalcification is exceedingly rapid in these patients, and calculi may form as early as four or five weeks after initial recumbency. This is particularly true if urinary infection has preexisted or has been introduced through catheterization at the time of acute illness. Patients who require catheterization shortly after onset of illness should be given full scale sulfonamide or antibiotic dosage until the status of the urine is established. Mobilization of the body, as with the rocking bed, is a step in the right direction in reducing skeletal decalcification, although it has not reduced the incidence of urinary calculi appreciably. High fluid intake, low calcium diet, and administration of alumina gels may be helpful in preventing urinary calculi. Urologic surgery frequently becomes necessary.

C. Nephrocalcinosis with Hypertensive Disease: The insidious low-grade hypertension which is common in bulbospinal poliomyelitis may progress and become associated with changes in the fundi, reduced renal function, arteriolar calcification, nephrocalcinosis, and hypertensive encephalopathy. The underlying cause is associated with hypercalcemia, and, until measures are developed for its prevention or alteration, it remains difficult to treat the effects of the clinical chain of events which ensues.

D. Emotional Problems: It is fortunate that the poliomyelitis virus does not invade the intellectual centers of the brain. The emotional problems of the severe poliomyelitis patient cannot be separated from those of his family's response to his illness. Counsel, including vocational and scholastic guidance, need not necessarily be psychiatrically oriented but must be given generously and repeatedly.[10]

CONCLUSIONS AND SUMMARY

Although no specific medicaments are available, it is encouraging to note improvement in the medical care of patients with poliomyelitis. The place for home care in the acute stage is discussed and attention devoted to the complicated hospitalized patients, particularly those with ventilation insufficiency. Improvement in the acute care of these patients stems from a union of close clinical observation and known physiological principles. Knowledge and anticipation of certain nonrespiratory complications which are enumerated may further reduce mortality and morbidity in the acute stage.

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Progress in Pediatrics

EARLY TREATMENT OF POLIOMYELITIS

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THE SUCCESS of the treatment of motor disability in poliomyelitis depends on proper management of the acute illness, on psychologic factors, and on orientation of the patient, his family, and all professional personnel concerned with his care. Unfortunately, during recent years the relatives of patients have indicated by questions and reactions that their connotation of the word "treatment" is limited chiefly to physical measures. The pediatrician or the internist who is meeting needs for hydration, electrolytes, and other such vital factors may save the patient's life or make him better able to tolerate and benefit by physical measures. All of us should help to educate the public to appreciate the crucial steps in early care, with recognition of the contributions by all consultants. The family physician should receive credit for being alert for symptoms, for asking for consultation when he needs help, and for arranging adequate early care so that the patient does not jeopardize his chances for recovery by exerting himself after onset, by delaying start of a constructive program, or by developing unnecessary limitations in joints and muscles.

The psychologic reactions of the patient may be guided favorably from the start if those about him use care in choice of words, tone of voice, or facial expression when he is seen at home or after he is admitted to the hospital. Too much emphasis must not be placed on muscle impairment, but rather interest should be aroused in self-reliance and school or occupational projects as soon as possible.

During the acute stage, examination of muscles and joints should be chiefly by inspection and palpation. A guarded range of gentle motion may be tolerated by some patients. Unnecessary handling and long examinations must be avoided.

In this paper, we shall not be concerned about discussing the well-known forms of physical treatment but instead shall emphasize certain practical points that may be overlooked or not fully appreciated. One of the chief problems in the acute stage, especially when there is little or no power in affected parts, is aching that comes from lack of movement of the body and associated sluggish circulation. We know from controlled experiments that the average person turns or moves in bed 12 or more times each night. If in the usual course of events one sleeps so soundly that there is little if any change of position, aching muscles and stiff joints may be expected without any illness. After trial of various forms of hydrotherapy, thermotherapy, and physiologic movements in poliomyelitis, we are most impressed by the effect of movement in relief of the aching, discomfort, and feeling of heaviness which is especially common in the patients having severe paralysis.

Read before the joint meeting of the Section on Pediatrics and the Section on Physical Medicine and Rehabilitation and the Section on Preventive and Industrial Medicine and Public Health at the 102nd Annual Meeting of the American Medical Association, New York, June 4, 1953.

Patients are not permitted to lie on their backs without being turned prone at alternate periods for at least half of the day. The prone position favors better lymphatic and venous flow from the region of the cord, besides relieving pressure on back muscles already sensitive and tense from meningeal irritation. Support is given under the coracoids at the shoulders, under the lower abdomen and hips, and at the ankles. This position may not be tolerated by patients with respiratory embarrassment, even if it is not severe enough to require the use of the rocking bed or the tank lung. Such patients are tilted from side to side and supported at a safe angle.

Correct positioning of extremities and movements of joints in patients who cannot use their muscles adequately help the flow of metabolic products along afferent pathways, discouraging phlebothrombosis seen in the past in patients with poor circulation from decreased skeletal muscle action, and tend to discourage adaptive tissue shortening which may initiate development of deformity. Alignment of affected parts, every two hours or more frequently, is in effect splinting. Children under 6 years who do not appreciate the importance of positions of physiologic advantage, should have light removable casts or similar support during the night and sometimes part of the day to offset the tendency toward deformity.

Patients with insult to motor-cell bodies in the medulla oblongata with resultant impairment of pharynx, vocal cords, or tongue may be able to keep the throat free from secretions best by the prone position if conscious and able to cooperate. Those who have encephalitis also, with lethargy and depressed vitality, or a second degree impairment of swallowing, may be so listless that the face is not turned to the side when prone, and observation may be easier and safer with the patient supported in various degrees of side-lying. In a third degree of dysphagia necessitating tracheotomy it is important that the head and trunk turn with equal pace when changing position. This attention helps to limit aching from inactivity in these patients and decreases undesirable passive congestion. Because of decreased depth of respiration accompanying extreme prostration, in changing from one side to the other there should be a pause on the back to permit expansion of the side of the chest that has been dependent, even when there is no paralysis of the diaphragm or intercostals. The electrophrenic respirator can stimulate better filling of the lungs when the patient cannot follow instructions to breathe or is so inactive that deep inspiration is not a natural automatic reaction.

In upper spinal poliomyelitis with weakness of chest muscles, it is well known that the patient in a tank lung, even in the most favorable circumstances, is at a disadvantage because of the restrictions imposed by the size and shape of the tank and the relative inaccessibility of the patient for change of position and movement of helpless parts. Tilting of the carriage stretcher at regular intervals and manual movement of trunk and extremities are beneficial but cannot be carried out with the same freedom as on the rapid rocking bed or on a regular bed. The chest respirator of the shell or cuirass type as well as manual movement of the rib cage can be used to mobilize the costovertebral joints, which are ignored too often.

PHYSIOLOGIC MOVEMENTS

Physiologic movements used as early as possible give one of the greatest aids to circulation and encourage restoration of muscle and joint function. Passive motion is tried first as soon as a painless arc is present. The affected part should

be lifted carefully, avoiding sensitive muscle bellies, and moved gently, stopping as soon as one feels the slight resistance to movement which occurs before the patient experiences pain and before the muscle offers reflex resistance or spasm. When a complete arc of passive motion is attained, proprioceptive stimulation may be brought into play. Stimulation of nerve endings in the tendon sheaths, intermuscular septa, joint linings, and periosteum by passive tension on a muscle and its attachments increases the patient's kinesthetic or muscle sense. Such proprioceptive impulses travel along sensory afferent pathways which are not involved primarily in poliomyelitis. Therefore we take advantage of them in passive movements to make the patient sense the location of the muscle for anticipated active effort.

MUSCLE REEDUCATION

When the temperature is normal and trial of voluntary use of a recovering muscle no longer causes quivering of muscle fibers, then reeducation is in order. The course of the muscle to be used is pointed out from insertion to origin, or, in small children, the skin over the muscle may be stroked in a similar direction. The instructor should be alone with the patient, and the full attention of the patient should be commanded. After indicating the course of the muscle, the physical therapist carries out the appropriate movement gently and rhythmically while the patient concentrates on the movement. After these preliminary maneuvers, the patient contracts the muscle while the movement is guided and assisted by the instructor. Initial effort is usually one active movement carried out several times a day according to the age and tolerance of the patient. Accuracy of effort and avoidance of substitution are important in these early days of convalescence. Obviously, the number of active movements and the frequency of exercise periods will vary according to the individual needs. An experienced physical therapist will combine reciprocal action (using agonist and antagonist) with individual muscle training when indicated.

RAPID ROCKING BED

The rapid-rocking bed, which we developed in 1945, saves many patients from entering a tank lung for respiratory aid and makes it possible to wean other patients from the respirator shortly after the onset of poliomyelitis. As the head of the bed rises, visceral shift favors inspiration. As the head of the bed drops, the abdominal organs migrate upward so as to help expiration. These two phases of movement make one respiration. The rate and range of the rapid-rocking bed must be estimated by the physician after careful observation and evaluation of each patient. The rate and range needed in the first minutes or hours the patient is on the bed may be greater than in a few days, when he has adjusted to the visceral shift and the diaphragm is more pliable. The initial use of the bed or exercise on it should not be after a meal. The patients soon learn to eat meals on the bed, swallowing as the head of the bed goes down. Talking and coughing are easiest during expiration, as the head of the bed goes down.

The patient enjoys the freedom of the rapid-rocking bed, feels less restricted than in the iron lung, and benefits from better circulation as well as easier respiration. During the past five years about 200, or an average of 40, patients needing respiratory aid have been seen each year. About half of each group had such severe impairment of breathing that the respirator was needed at once as a life-saving

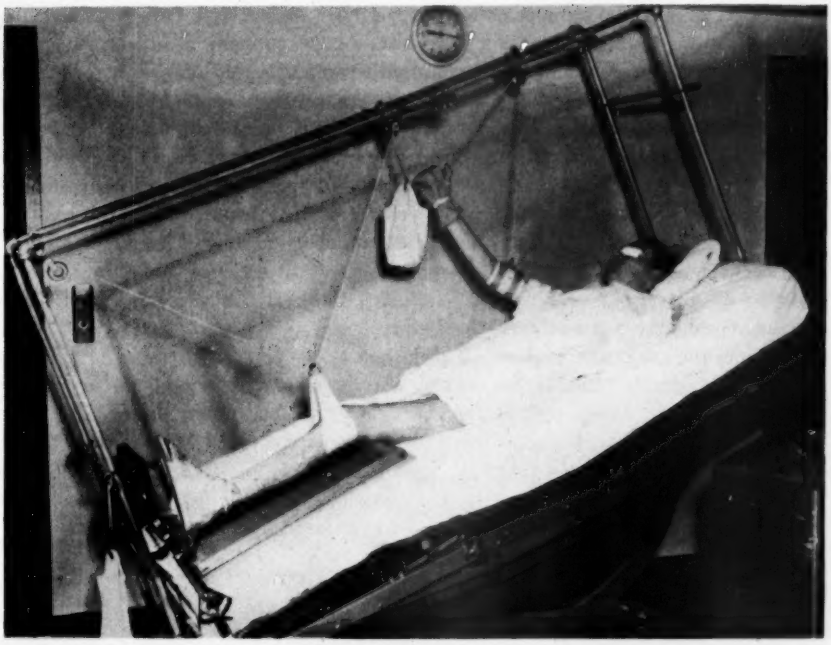

Fig. 1.—As the head of the rapid-rocking bed rises, helping inspiration, the momentum is used to advantage for passive or active assisted exercise to retain range of motion, stimulate muscle sense, and improve circulation.

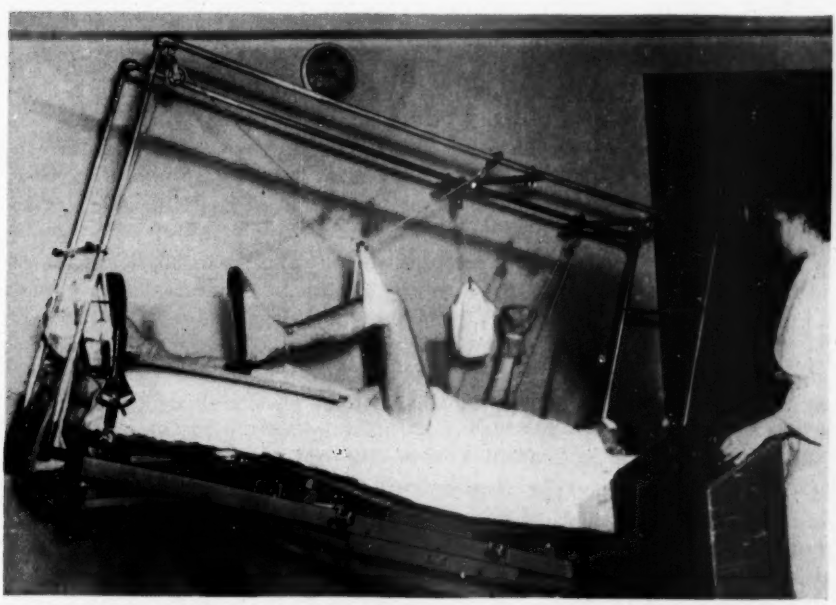

Fig. 2.—As the head of the rapid-rocking bed falls, favoring expiration by visceral shift, the extremities go into another phase of movement.

measure. The others responded to the help of the rapid-rocking bed, which can be adjusted to the desired respiratory rate. Each of the patients in an iron lung was weaned from it by use of the rocking bed. All patients were finally able to breathe adequately on a regular bed with the head posts raised about 6 in. (15 cm.). Patients who could breathe well without rocking were kept on the bed when extensive involvement of arms, legs, and trunk was present to reduce passive congestion and facilitate blood flow in the absence of the usual aid given by contraction of skeletal muscles. The patients remarked about relief from stiffness and aching and the greater ease of movement while the bed was rocking rapidly. The momentum of the bed makes passive or active movement of weak affected parts easier. Assisted, unassisted, or resisted exercises may be carried out, taking advantage of the two phases of bed movement in each respiratory cycle.

Besides the use of the momentum of the bed by the physical therapist to mobilize joints and reeducate muscles, the rocking may be adapted to functional activity by the use of frames, ropes, pulleys, weights, gloves, and skates or gliders (Fig. 1). The left arm may be arranged to move forward with the right leg as in the alternation of walking (Fig. 2). In this way, habit patterns may be started in the subacute and early convalescent stages. Also, the proprioceptive stimulation arouses kinesthetic sense and is a source of interest and encouragement to the patient.

OBJECTIVES OF PHYSICAL THERAPY

Besides relief of pain, the object of any physical treatment must be to improve circulation, thus mobilizing products of metabolism which have been locked in tense muscles and facilitating replacement by fresh arterial blood bringing nourishment and oxygen to aid in restoration of metabolic balance.

Since measures to improve circulation in recent years have been instituted early after onset, few problems in vasomotor or trophic disturbances arise. When there is any suggestion of impairment of capillary filling with sluggish blood flow, in the absence of cardiovascular disease, use of a vasodilator and the rocking bed has a favorable influence. For example, benzazoline (Priscoline) hydrochloride produces vasodilatation and increases peripheral blood flow by counteracting the constrictive effect of epinephrine-like substances at the vascular myoneural junctions. The rapid-rocking bed helps to compensate for diminished skeletal-muscle contraction in impaired groups, thus aiding circulation.

After the use of sedative and decongestive applications plus physiologic movements in the subacute stage, a transition may be made to more tonic measures, such as underwater exercise, contrast baths or sprays, massage, and functional activity. Self-help should be encouraged, so that the patient who necessarily has had constant attention during the critical days of illness may turn from excessive dependency to as much independence as his residual weakness and physical disability allow.

OCCUPATIONAL THERAPY

The occupational therapist cooperates with the nurse and the physical therapist in encouraging a philosophical attitude, emotional stability, motivation for physical restoration, and psychologic adjustment. Arts, crafts, and skills may go far beyond primary activities in arousing secondary responses related to self-confidence, independence, and satisfaction of accomplishment. In the acute stage, the occupational therapist may help to prevent restlessness and assure ease of mind by such

diversions as music, reading to the patient, or relieving anxiety of adults by keeping them occupied. The discreet medical social worker may share these opportunities to make the illness less of a trial to the patient and relatives and establish understanding between the professional personnel and the family about personal problems that arise. Materials used for diversion should be chosen so that they can be destroyed or sterilized. In the early convalescent stage the occupational therapist, with the psychologist, may investigate the patient's aptitudes and interests, following which investigation functional therapy may be adapted to individual needs. Older patients may be guided toward interest in return to school or to prevocational therapy related to previous or planned work.

After the acute stage, occupational therapy is most useful if directed to functional activity of the hands and arms, while physical therapy is concentrated on function of the legs and trunk, as well as on locomotion.

TRANSITIONS IN TREATMENT

Packs or curare, either of which may have a limited use in the acute stage in preparation for physiologic movements, should be discontinued as soon as tense, irritable muscles have relaxed enough to permit a full arc of passive motion. Then exercise and functional activity to meet daily needs are more important.

Muscles that show no trace of active response after the early weeks of paralysis should receive properly dosed electrical stimulation. This procedure favors better physiology in contractile parts of muscle, thus assuring pliability and better circulation, besides reminding the patient of the course of the muscle and how it feels when it contracts. The patient watches as the muscle responds to the current. The second time the muscle is stimulated, the patient tries to use the muscle with the help of the current. The third time with assistance he tries to contract the muscle without the current. This helps to establish a pattern of movement which discourages substitution. We are interested at first in patterns of movement instead of individual or general muscle strength.

While attention to extremities is taken for granted and handled well for the most part, not enough recognition is given to problems related to the trunk. Asymmetric tightness or weakness in back or abdominal muscles may lead to scoliosis in spite of expert supervision. Mobilization of facets limited more on one side of the spine than the other, localized muscle reeducation of strips by voluntary effort or electrical stimulation, special braces, and careful training in good posture should follow as a matter of course. Fascial grafts as devised by C. L. Lowman, of Los Angeles, may be used early if muscles do not respond in a reasonable time. This internal splinting controls certain asymmetries better than any exercise or external brace.

If the trunk has bilaterally symmetrical weakness, mobilization of the spine, especially rotary movements for the facet joints and related muscles, may be justified if the average grade of power becomes fair or better. Some patients who take the trouble learn to balance themselves in a remarkable fashion. But in the presence of less than fair power in a person who will be under stress at school or work, careful study may suggest that the patient will have more stability if the spine is not made more limber but is braced in a position to favor stiffening and security. Later the orthopedist may suggest operative procedures which will help the patient.

In study of the back, one should bear in mind the distorting effect of a small buttock in sitting or a short leg in standing. Also some of the deviation or abnormality present may not be due to the paralysis, but may be on another basis, such as a congenital defect requiring different analysis and treatment.

When the question of change from the lying to the weight-bearing positions arises, one should consider not only muscle balance but also influence of the weight of the part, gravity, and related static strain. In the transition from sitting to walking, various devices are helpful for standing, balancing, and locomotion. Special adjustments on stationary and moving bicycles, crutches for propelling the body in a sitting position on a mat, progression from chair to floor, from standing to floor and return, besides instruction in appropriate gaits for easy walking, for crossing streets, for climbing and descending stairs, using crutches or canes as needed, challenge the ingenuity and insight of the physician. We continue to work on special devices to improve functional activity of the hands and arms.

SUMMARY

Early treatment of poliomyelitis is ordered according to the tolerance of the patient and the type and distribution of the paralysis. An appreciable percentage of disability may be due to poor circulation adding to the insult of virus and toxins or giving secondary effect in all systems of the body. Assuring the best physiologic response possible in circulation, muscles, joints, and neuromuscular pathways will aid recovery toward useful function. Psychological, emotional, educational, and vocational guidance should be the concern of all physicians seeing the patient from the onset of illness.

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ABSTRACT OF DISCUSSION

Dr. Duane A. Schram, Gonzales, Texas: In comment I shall emphasize only the treatment measures brought out so well in Dr. Wright's excellent paper, "The Early Treatment of Poliomyelitis." Actually, the treatment used in postacute poliomyelitis is based upon the concept of judiciously balancing activity with inactivity. It is extremely important in the early care of this disease to insist upon sufficient rest and during these inactive periods to keep the patient in as near physiological alignment as possible. As the time from the onset increases, so does the amount of activity. Early, the activity is primarily one of mobilization. This is the primary objective found in passive motion and in frequent change of position. Later, in early muscle reeducation, these passive movements develop into active motion and then eventually into specific strengthening exercises.

As the tempo of all activity increases, it eventually evolves to one of function. The preparation has been to recover all strength remaining in the affected neuromuscular units and at the same time attain or maintain normal body alignment. As the patient concentrates on learning purposeful movements, we find that the goal through graduated activity is maximum functional capacity.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Alfred S. Traisman, President
Regular Meeting, Nov. 17, 1953

Gargoylism. Dr. Philip L. Aries.

A 23-month-old baby girl was admitted to the Mount Sinai Hospital on Oct. 8, 1952, because of a minor head injury, the symptoms of which promptly subsided. It had been noted that growth and physical and mental development were retarded. The parents were well. They were not related before marriage. They had one older normal child. The mother had a normal pregnancy before the delivery of this baby. The labor was uneventful. The baby weighed 6 lb. 10 oz. (3,000 gm.) at birth. The breathing had always been noisy because of a constant nasal discharge.

On physical examination the head was elongated in the anteroposterior diameter. The bridge of the nose was depressed under a prominent forehead. The pupils were normal. A cloudiness of the cornea was detected during an attempt to make a funduscopic examination. The heart and lungs were normal. There was a marked enlargement of the liver and spleen. The extremities appeared to be comparatively short. There was limitation of extension of the finger joints.

X-ray revealed the skull to be scaphocephalic. The sella turcica was widened. The metacarpal bones were short and thick. Irregularities and deformities of the vertebrae were noted.

The blood and urine were normal. Marrow from the tibia was histologically normal.

The diagnosis made was gargolyism, or Hurler's syndrome. The disease is of congenital origin and believed to be due to the storage in the tissues of a complex substance which is a combination of glycogen and protein.

Anaphylactoid Purpura Treated with Cortisone. Dr. Jeanette Hork.

J. L., a 21-month-old boy of known allergic tendency, became ill on July 29, 1953, with a temperature of 102 F., a rash in the diaper area and upper thighs, and swelling of the dorsum of both feet. Two weeks previously he had had a severe follicular tonsillitis with high fever, which was treated with penicillin (300,000 units intramuscularly and 600,000 units orally) with good response in 24 hours.

Initial examination, on Aug. 1, 1953, revealed a recurrence of the follicular tonsillitis with an accompanying redness and edema of the surrounding pharyngeal tissues. There was a nonpitting edema of the feet and of the left knee. The diaper area and upper thighs were covered with many deep-pink flat urticarial papules the size of a split pea.

Oral penicillin was prescribed, but 24 hours later the lesions had spread to the legs, the arms, the feet, the external ears, the mucous membrane of the palate and gums, the cheeks, and the chin. There was extensive edema of the left elbow and of the scrotum and perineum, with petechiae in the scrotal skin. The lesions were now coin-sized, markedly indurated, and bright purple in color. The temperature was 103 F.

Initial blood cell count showed RBC 5,010,000; HGB. 10.8 gm. per 100 cc. (69%); WBC 23,700, with 76% segmented cells, no eosinophiles, 4+ toxic granulations, platelets 103,000. Bleeding and coagulation time were normal. Stool and urine were negative for blood.

Bone-marrow puncture revealed evidence of a severe pyogenic infection with moderate thrombopenia and an increase in eosinophiles. There was no evidence of acute leukemia.

Chlortetracycline (Aureomycin) was given for 24 hours with no clinical improvement and with the subsequent onset of diarrhea. Penicillin was again administered, 200,000 units orally every three hours. Cortisone was begun in doses of 50 mg. orally, every six hours. After two days, the lesions and edema disappeared. Subsequently, each time the dose of cortisone was reduced, the lesions recurred, but were increasingly smaller and pink rather than purple. After 11 days, cortisone and other medications were discontinued. The temperature and

white blood cell count had gradually dropped to normal. There was a slight recurrence of pinhead-sized lesions on Aug. 31, 1953. The patient has remained well except for allergic rhinitis. There are a few pigmented areas on the arms and legs.

Encephalitis Preceding Mumps. DR. MAXWELL P. BOROVSKY.

This 6-year-old boy was admitted to the hospital because of fever, severe headache, vomiting, increasing stupor, grinding of teeth, and yawning for two days prior to admission. When seen at the hospital, he was in a deep stupor, from which he could be aroused only with strong stimuli. There was a slight nuchal rigidity, but negative Kernig's and Brudzinski's signs. A diagnosis of virus encephalitis was entertained and seemed confirmed by the spinal-fluid finding of 28 cells, almost all lymphocytes. There was a slightly positive Pandy's test, protein 51 mg. per 100 cc., chlorides 617 mg. per 100 cc., and sugar 85 mg. per 100 cc.

Eighteen hours after admission and about three days after the onset of the illness, he dramatically developed a rapid bilateral parotid swelling. The diagnosis thus established improved the prognosis.

The suggestion is made that all cases of encephalitis of undetermined origin be considered of a mumps etiology. In verifying this suspicion, a history of a previous attack of mumps or of a recent exposure would be of great value. A complement fixation test will be of help in a case that does not have a manifest parotitis. The shortcoming of this latter procedure is the late appearance of the antibodies, usually 7 to 14 days after the onset. The mumps neutralization test is considered by many to be more reliable than complement fixation and may be determined earlier in the course of the disease.

Tracheoesophageal Fistula and Other Abnormalities. DR. SAMUEL SCHWIED.

This "post-Caesarean" white premature boy (37 weeks), weighing 4 lb. 6½ oz. (2,000 gm.), was born on July 5, 1953, appearing normally developed. The baby had shallow breathing, and the respiratory tract appeared full of mucus; the condition apparently was poor.

During the next three days, the infant experienced respiratory difficulties, cyanosis, and a severe attack of apnea followed by large amounts of coffee-ground material exuding from the nose and mouth and severe substernal and intercostal retractions. Meconium was passed; copious mucus, then bright red blood was discharged from the nose and mouth. A mass in the left flank appeared July 7, enlarged, and filled all of the abdomen by July 8; no bowel sounds were heard. A Levin tube was passed, and only small amounts of tenacious dark blood exuded.

An exploratory operation was performed anticipating obstruction and perforation. Free fluid was noted, and drainage was instituted. A sketch of the anomalies, drawn at this time, corresponded to those at autopsy. The baby died on July 10, 1953.

X-ray findings on July 8, 1953, were compatible with stenosis or atresia of the duodenum and a hollow viscus perforation; pneumoperitoneum was present.

Autopsy revealed esophageal atresia, upper part; tracheoesophageal fistula; perforation of the fundus of the stomach; stomach dilated, ending in blind pylorus; duodenal atresia, and additional findings of pulmonary atelectasis and hyperemia, subarachnoid hemorrhage, and extensive intraventricular hemorrhage.

Refractory Rickets. DR. I. MICHAEL LEVIN.

This is the case of a 12-year-old girl with rachitic bone changes refractory to usual vitamin D administration. She is the first-born of a frail mother of short stature, who had no extra mineral or vitamin D intake during pregnancy. The infant's birth weight was 6 lb. 11 oz. (3,030 gm.), at 5 months, 15 lb. (6,800 gm.); she received a well-balanced diet plus 15 drops of percomorph liver oil daily (10,000 units of vitamin D).

She walked at 16 months, and bowing of legs was well marked at 18 months; roentgen studies showed moderate bowing of the left and right tibiae with increased thickness of the cortex of the medial side of the tibiae and slight flaring of the proximal as well as the distal epiphyses, the latter showing cupping.

There was no improvement in appearance of legs or roentgen views with change in vitamin D preparation and increase to 15,000 units daily; the lower extremities were flexible. At

28 months, there were 17 teeth, and the ribs were smooth; at 30 months there was marked cupping of the lower femurs and tibiae. Vitamin D dosage increased to 50,000 units daily plus dicalcium phosphate; at 32 months there was marked calcification in the epiphyseal areas of the lower extremities (healing).

At the end of the next 18 months, the legs had straightened so that bowing was not apparent at 4½ years (January, 1946). In October, 1947, a peculiar fraying and cupping of the epiphyseal lines of the femurs and tibiae was seen. Vitamin D dosage had been decreased. Blood calcium, phosphorus, nonprotein nitrogen, ascorbic acid, and Kahn test were normal, but alkaline phosphatase was 12.3 units. No renal pathology was evident.

Varying degrees of cupping and bone change continued. In the spring of 1953 (age 12 years), bowing of lower extremities became more apparent, with associated scoliosis of the dorsolumbar spine. There has been a spurt in growth and development of secondary sex changes. Roentgen findings are indicative of rachitic changes with alkaline phosphatase 10.9 units.

Letterer-Siwe Disease. DR. JULIUS ARONOW.

This 18-month-old white boy was hospitalized because of a skin eruption of eight months' duration involving the neck, scalp, back, and chest and x-ray evidences of pneumonitis. There was no previous history of any illness. Birth and development were normal.

Physical examination revealed a moderately well-nourished infant, with a temperature of 102.4 F., pulse 128 per minute, and respirations 28 per minute. The entire back, scalp, and anterior chest were covered with diffuse pink maculopapular and erythematous pinhead-size lesions with dry white scales. Nose and throat cultures revealed large numbers of Pseudomonas aeruginosa. Pseudomonas was also cultured from material taken from an ulcerative lesion in the right axilla and from tracheal aspiration.

No acid-fast bacilli were found. Mantoux 1:1000 and histoplasmin test were negative. Chest x-ray showed pneumonitis with numerous small soft nodules compatible with a Pseudomonas infection. Neomycin therapy was initiated, and a repeat x-ray taken 10 days later was interpreted as indicative of improvement. The right axillary ulcer had healed, and the patient was discharged.

The impression at this time was that of eczematoid dermatitis with superimposed Pseudomonas infection and pneumonitis.

The child was readmitted Oct. 6, 1950, extremely toxic, dehydrated, and cyanotic; respirations were 68, temperature 98.6 F., and pulse 130.

The impression given was that of a severe bronchopneumonia with overwhelming sepsis.

Cultures from the ears and nose revealed hemolytic Staphylococcus aureus; blood culture was negative. An axillary ulcer showed Ps. aeruginosa. Therapy consisted of balanced parenteral fluids, multiple vitamins, whole-blood transfusions and antibiotics. X-rays revealed bilateral central pneumonia with a "snow-storm picture." The liver edge was 3 cm. below the right costal border. The child improved.

Fever reoccurred on Oct. 20, 1950, and x-rays revealed a diffuse interstitial pneumonitis. Stools showed high neutral fat residual. Gelatin digestion was negative for trypsin. Fibrocystic disease of the pancreas was strongly considered.

The subsequent course was downhill, the spleen became palpable 3 cm. below the left costal margin. Despite supportive therapy, the child died on Dec. 17, 1950.

The pathological report showed the following: (1) gross—cystic disease of the lungs with chronic organizing pneumonia; (2) microscopic—nonlipid reticuloendotheliosis (Letterer-Siwe disease) in the skin, lymph nodes, thymus, lungs, liver, spleen, and bone marrow.

Congenital Heart. DR. BENJAMIN GASUL.

S. B. was first examined on March 23, 1953, with a history of heart murmur noted at the age of 3 months and cyanosis of lips, fingers, and toes at the age of 6 months. Since that time his cyanosis has been increasing and his physical activity was markedly restricted, walking across the room causing him to squat for recovery.

Physical examination revealed a 6-year-old white boy with marked cyanosis and clubbing of the fingers and toes and dyspnea upon walking across the ward. His weight was 39½ lb.

(17.9 kg.), pulse rate 88, and respirations 34 per minute. The cardiac apex was in the fifth interspace 1 cm. outside the midclavicular line. A loud Grade-4 systolic murmur was heard over the second and third left interspaces; the second pulmonic sound was equal to the second aortic. Femoral pulsations were normal. Blood pressure in the upper extremity was 120/80; in the lower extremity, 135/80.

Fluoroscopic and roentgen-ray examinations revealed diminished pulmonary vascular markings, straightening out of the pulmonary area, a right aortic arch, and right ventricular hypertrophy.

Electrocardiogram revealed right ventricular hypertrophy.

Slides demonstrate the angiocardiographic and catheterization findings.

The diagnosis was tetralogy of Fallot with right aortic arch.

The conclusion reached was that a tetralogy of Fallot may have poststenotic dilatation of pulmonary arteries and that the posteroanterior view of the heart may show a bulge in the pulmonary area instead of a concavity. The aortic window (incorrectly called the pulmonary window) is not wide in these patients and appears to be normal.

Subcutaneous Fat Necrosis with Secondary Calcification. Dr. Max Shein.

An unusual case of calcification of the subcutaneous fat is presented.

A white baby boy, 8 weeks old, was admitted to Mount Sinai Hospital because of the presence of extensive areas of subcutaneous induration. The past and familial history are not important.

The infant did not appear acutely ill. He was well nourished and well developed, with normal physical findings, except for the mentioned areas of induration. They involved the posterior surface of the chest, and the lumbar and sacral regions, as well as the buttocks and flexor surfaces of the lower extremities, without involvement of the articulations. The skin of the areas involved was bluish in color and of a woody consistency, with no pitting on pressure.

Hematologic and blood-chemistry studies revealed no abnormalities.

Roentgen studies of the lower extremities and pelvis showed an amazing degree of deposition of calcium in the subcutaneous tissue in diffuse and regular distribution, mainly located at the flexor surfaces of the legs and thighs and over both buttocks.

Biopsy revealed normal epidermis and corium. The epidermal fat showed multiple areas of calcification surrounding and inside the fat cells, with foreign-body reaction—fibrosis and giant-cell formation.

The infant remained in the hospital for one month, during which time there was some improvement, with disappearance of the induration in the chest and lumbar region and slight softening of the tissues in the buttocks and lower extremities.

A balanced diet and vitamins were given. No specific treatment was administered. The infant is now being followed in the outpatient department.

This case has been diagnosed as one of calcinosis circumscripta, as defined by Potter and Caffey, differentiated from calcinosis universalis, adiponecrosis subcutanea neonatorum, sclerema, and scleroderma.

Lobar Emphysema. Dr. Samuel J. Bolonik.

This infant was delivered by low forceps and cried spontaneously. He weighed 8½ lb. (3,860 gm.), color was good, respirations were regular, and no abnormalities were found.

At 2 weeks of age the mother noticed that the infant's respiration was rapid and the color of the skin was not its usual pink. Examination at that time revealed an infant that was dyspneic and cyanotic. Neither auscultation nor percussion revealed any abnormalties, but on fluoroscopy it was found that the mediastinum was shifted over to the right. Electrocardiographic and x-ray findings indicated that we were confronted with pulmonary pathology, rather than a congenital heart. Bronchoscopic examination revealed the left main bronchus to be obstructed by compression.

The infant was submitted to surgery. Immediately after the chest was opened, the emphysematous upper lobe bulged out of the wound. No abnormality of the bronchus could be found from the outside. The upper lobe was then removed, and the child made an uneventful recovery.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

NUTRITIONAL INTAKE OF CHILDREN. VIRGINIA A. BEAL, J. Nutrition **50**:223 (June 10) 1953.

The author has presented data from 604 nutrition histories on 46 children in the first five years of life. Calory, carbohydrate, fat, and protein intakes, referred to age and to body weight, have been computed in terms of quartiles and maximum and minimum intakes. Of particular interest are the comparative rates of increase in the total intake of the four nutrients and the clarity with which they reflect the eating problems so commonly encountered with the preschool child. During the first 15 to 18 months, the rise in intake of protein is most marked, that of carbohydrate and fat less marked. There follows a stationary level of protein intake, while carbohydrate and fat intakes continue a slow but steady increase, until shortly after three years, when protein again reveals an ascending curve. Calory intake is, of course, a composite of these three nutrients and shows only a slight increase between 18 months and 3 years.

The preschool period has long been accepted as an interval in which the child presents a number of problems in eating. There is a lag in appetite, an indifference to foods, and outright refusal for some foods. From her experience, Beal states that the most marked decrease is in the consumption of milk and vegetables. The age of onset of poor appetite varies from one child to another, being most often between 9 and 18 months, but occasionally later, and the duration varies from a few months to more than two years.

The median calory intake is close to the recommended dietary allowance of the National Research Council, the median protein intake is above the recommended dietary allowance in the first two years and thereafter is similar to the allowance. Intake of protein per kilogram of body weight shows a consistent decrease in this age period. The descending curve of intake of calories, carbohydrates, and fat per kilogram of body weight is interrupted by a temporary rise in the second year.

FREDEEN, Kansas City, Mo.

THE RELATION OF CALCIUM-TO-PHOSPHORUS RATIO TO THE UTILIZATION OF THESE MINERALS BY EIGHTEEN YOUNG COLLEGE WOMEN. M. B. PATTON, E. D. WILSON, J. M. LEICHSENRING, L. M. NORRIS, and C. M. DIENHART, J. Nutrition **50**:373 (July 10) 1953.

Eighteen normal healthy young women served as subjects in a calcium-phosphorus balance study designed to determine the effect of varying the ratio of calcium to phosphorus upon the balances of these two minerals. The mean calcium balances varied from -46 to $+196$ mg. and the mean phosphorus balances from -64 to $+86$. When phosphorus was kept constant, an increase in calcium intake resulted in a significant increase in calcium balance. With constant phosphorus intake, phosphorus balances were not affected by an increase in calcium intake. Patton and co-workers concluded that the balances of both minerals were more closely related to intakes than to the ratios of calcium to phosphorus. The absolute amount of urinary calcium increased with increased intake, but the percentage of intake found in the urine decreased with increased intake.

FREDEEN, Kansas City, Mo.

DISTRIBUTION OF THE XANTHINE OXIDASE FACTOR (MOLYBDENUM) IN FOODS. W. W. WESTERFELD and DAN A. RICHERT, J. Nutrition **51**:85 (Sept. 10) 1953.

In general, foods containing relatively large amounts of molybdenum were (1) most cereals and grains, (2) legumes, and (3) some dark-green leafy vegetables. Animal tissues highest in molybdenum included liver, kidney, and spleen; muscle meats and fish contained little molybdenum. Fruits, berries, and most root or stem vegetables were relatively poor sources of molybdenum. Brewers' yeasts were good sources, and bakers' yeasts were poor sources.

FREDEEN, Kansas City, Mo.

BLOOD GALACTOSE IN INFANTS AND CHILDREN. A. F. HARTMANN, E. GRUNWALDT, D. H. JAMES, and M. K. MORTON, J. Pediat. **43**:1 (July) 1953.

Ordinarily as much as 40% of the blood sugar of milk-fed infants may be galactose. When such infants are given large amounts of galactose, for example, 1.75 gm. per kilogram of body weight, the blood-sugar curve rises in a manner similar to that of a normal glucose tolerance test, with the exception that the rise is due entirely to galactose. During the early rise of galactose, the glucose may fall and then rise later as galactose falls. Normal infants receiving no lactose- or galactose- containing food show no galactose in the blood. In these infants, normal values for glucose may be expected. In infants with galactosemia, receiving lactose or galactose feedings, abnormally high values of blood galactose may be expected, and if galactose and glucose are not separately determined, hypoglycemia may escape detection. These infants may show small amounts of galactose in the blood even when not receiving lactose- or galactose-containing food. This suggests the formation of galactose from glucose. In infants with diarrhea, when fed milk after a period of starvation or nonmilk feeding, high blood galactose values may mask hypoglycemia, unless glucose and galactose are individually determined. The high blood galactose values seen in such infants, even while underfed, suggest temporary partial "galactosemia," perhaps the result of illness and milk deprivation.

The authors discuss the metabolism of galactose and outline their method for distinguishing the amounts of galactose and glucose in blood samples.

MACDONALD, Pittsburgh.

TOTAL AMINO ACID COMPOSITION IN MATURE HUMAN MILK: ANALYSIS BY THE ION EXCHANGE RESIN COLUMN CHROMATOGRAPHIC TECHNIC. MUNG W. CHAUNG, EDWARD L. PRATT, and DOROTHY I. FOWLER, Pediatrics **12**:353 (Oct.) 1953.

Values for total amino acids in two pools of mature human milk, consisting of milk from nine and five individual mothers, have been determined by the ion-exchange resin-column chromatographic technique.

Two unidentified ninhydrin-reactive substances and 3-methyl histidine are found to be present in significant amounts in whole human milk.

FROM THE AUTHORS' SUMMARY.

A NEW APPROACH TO INFANT FEEDING. W. F. GOUGH, Canad. M. A. J. **68**:544-545 (June) 1953.

The author advocates a radically early introduction of solid foods. He starts orange juice at 7 days, cereal at 7 days, fruit at 12 to 14 days, meat and vegetables at 21 days, egg yolk as soon as the meat is well started, and egg white soon after that. By six weeks the infants will be eating everything, are likely to be on whole cow's milk, and some of them will be drinking from a cup. The author feels that this routine has resulted in 75% fewer sick children, no feeding problems, and generally superior health in the preschool years.

McGUIGAN, Evanston, Ill.

OBSERVATIONS ON NUTRITIONAL DYSTROPHY. S. T. ACHAR and C. BENJAMIN, Indian J. Child Health **2**:1 (Jan.) 1953.

Studies by the authors show that nutritional dystrophy forms about 9% of the total admissions in the pediatric service in Madras. Age incidence is mostly between 1 and 5 years. The condition differed from the kwashiorkor of Africa mainly in the prevalence of vitamin A deficiency. Hypoproteinemia and reversal of the albumin-globulin ratio was a constant feature. Blood transfusions are of great value, and high protein diet is essential.

McGUIGAN, Evanston, Ill.

PSYCHOLOGICAL ASPECTS OF FEEDING PROBLEMS IN CHILDREN. J. C. MARFATIA, Indian J. Child Health **2**:156-160 (April) 1953.

The author briefly discusses the psychological aspect of feeding problems. His approach is practical, sensible, and intelligible.

McGUIGAN, Evanston, Ill.

TREATMENT OF INITIAL AND SECONDARY HYPOGALACTIA. H. CZERMAK, Ann. pædiat. **180**:28 (Jan.) 1953.

In spite of the great progress made in artificial infant feeding, there can be no doubt that breast feeding during the first months of life is the only perfect method of feeding. The propagation of this fact should be the aim of prophylactic pediatrics. A deficient inability to breast-feed as a general phenomenon does not exist. Excellent results are reported from Vienna, where experts have been dealing efficiently with hypogalactia, which in its primary form is only an initial symptom and in its secondary form a passing one. Ways and means are pointed out to be taken in wards with newborn babies and maternity homes in order to achieve this goal.

FROM THE AUTHOR'S SUMMARY.

COMPARATIVE INVESTIGATIONS OF THE ENZYMATIC SPLITTING OF VARIOUS KINDS OF STARCH. MARIANNE LOES, Ann. pædiat. **181**:1 (July) 1953.

Extensive and methodical investigations of the digestion of starch with the aid of pancreas amylase were carried out and later on comparative experiments were done with the same method on potato, maize, rice, barley, rye and oatmeal starch. Contrary to the results which have so far been published, it could be shown that with equal experimental conditions only potato starch is digested more quickly and extensively than the starch of all the bread grains which reached the same degree of digestion and reached this degree at the same speed. The time necessary to boil starch paste had no influence on the speed of digestion.

FROM THE AUTHOR'S SUMMARY.

PERSISTENT FAMILIAL PHOSPHORUS DIABETES WITH VITAMIN D-RESISTANT RICKETS. P. SCHMUZIGER, Helvet. pædiat. acta **8**:276 (June) 1953.

There is evidence of considerable disturbance in the calcification of the dentine, inasmuch as the organic substance between the globuli is insufficiently calcified. This process is part of the disturbances caused by rickets. Enamel and dentine are very underdeveloped in volume. No subsisting of this inadequacy in calcification can be observed, and histological examination reveals that the deficiency is most pronounced in the layers of dentine formed last. While this misdevelopment is of internal nature, the external structural changes in the enamel commonly observed in rickets (hypoplasias) are absent.

FROM THE AUTHOR'S SUMMARY.

THE ACTION OF OXYTETRACYCLINE (TERRAMYCIN) IN INCREASING BODY WEIGHT. M. GOMIRATO SANDRUCCI, Minerva pediat. **5**:699 (Aug. 31) 1953.

Mice receiving 0.24 mg. oxytetracycline (Terramycin) per kilogram of body weight daily in addition to their regular diet had a more rapid growth and development than control animals. A much higher dose led to diarrhea and retarded development. A smaller dose was ineffective. The more rapid growth may have been due to a more efficient fecal flora, to the supplementing action of the drug on the vitamin B_{12} metabolism, or to better utilization of protein. The suggestion is presented that oxytetracycline may have a beneficial clinical application in nutritional cases in children.

HIGGINS, Boston.

Vitamins; Avitaminoses

AGEWISE DIFFERENCES IN THE URINARY EXCRETION OF VITAMIN B_{12} FOLLOWING INTRAMUSCULAR ADMINISTRATION. D. M. WATKIN, C. A. LANG, B. F. CHOW, and N. W. SHOCK, J. Nutrition **50**:341 (July 10) 1953.

These studies present evidence only on the urinary excretion of vitamin B_{12} administered parenterally in young and old. The subjects, 107 persons in widely separated age categories, were given the vitamin at 20, 30, 50, and 75 μg dose levels. The data showed that the amount of B_{12} excreted increased progressively with increasing dose and that at all dose levels the aged subjects excreted less of the administered vitamin than did the young. The decrement in B_{12} excretion with age parallels decrements in renal function with age. However, so small a fraction of administered B_{12} appears in the urine that the observed differences cannot be attributed to renal factors alone.

FREDEEN, Kansas City, Mo.

TWO NEW CASES OF ACUTE BENIGN HYDROCEPHALUS DUE TO MASSIVE DOSES OF VITAMIN A. NIETO FERRARO, Acta pediat. españ. **11**:350-352 (March) 1953.

The author presents two unreported cases of acute benign hydrocephalus in infants and expresses the opinion that this condition may be produced either by water-soluble or fat-soluble products. The difference he feels is only in the rate of absorption.

ALLEN, Santa Fe, N. Mex.

RICKETS AND VITAMIN D ENRICHED MILK. HORST PRENZEL and HANS-ARNOLD SIMON, Monatsschr. Kinderh. **101**:397-402 (Sept.) 1953.

During the years 1950 and 1951, the entire milk supply of the German city of Oldenburg was fortified with an alcoholic solution of vitamin D_3, 1,000 units per liter. All infants born during 1949, 1950, and 1951 were examined for evidence of rickets, and a statistically significant decrease in the occurrence of the disease was found.

HARTENSTEIN, Syracuse, N. Y.

Hygiene; Growth and Nutrition; Public Health

MAXIMUM BREATHING CAPACITY AND VITAL CAPACITY IN FEMALE CHILDREN AND ADOLESCENTS. B. G. FERRIS JR. and C. W. SMITH, Pediatrics **12**:341 (Oct.) 1953.

Expected mean values and a range of normal values (plus or minus twice the standard deviation) are presented for the vital capacity and the maximum breathing capacity of female children and adolescents.

Although multiple correlation does not demonstrate a particularly higher degree of predictability, it is recommended that the above values be based upon the four attributes (age, height, weight, and body surface area), rather than upon a single attribute. This is especially important in the abnormally shaped person.

FROM THE AUTHORS' SUMMARY.

ILL-HEALTH AMONG SCHOOL CHILDREN WHO HAD PREVIOUSLY ATTENDED DAY NURSERIES. LENNART HESSELVIK, Acta pædiat. **42**:491 (Nov.) 1953.

An investigation has been carried out in order to examine whether the frequent infections occurring in children cared for at day nurseries had any significant effect on subsequent ill health during the early school years. The study was made on a series of children who had been the subject of an investigation four years earlier. It had been found previously that a substantially higher sickness rate prevailed among children in day nurseries, and also to a certain extent among nursery school children, than among those cared for exclusively at home.

Among the common specific infections of childhood it has now been found, as expected, that measles occurred more frequently among the children formerly at home than among the former day-nursery children, the latter having already had the disease before starting school. Nonspecific diseases (chiefly respiratory infections and their sequelae) were found to occur to more or less the same extent in all the three groups. Attendance at these types of institutions must therefore be assumed to have no great influence on the later occurrence of these conditions.

Among the children investigated, ill health due to nonspecific causes was found to occur at about the same level in all groups, corresponding to about 5% absence. No definite correlation could be established between ill health recorded four years earlier and the frequency of absenteeism of the same persons reported during the period of the present investigation.

FROM THE AUTHOR'S SUMMARY.

SOME POINTS OF VIEW ON INFANT MORTALITY IN NORWAY. ALFRED SUNDAL, Tidsskr. norske lægefor. **72**:339 (June 1) 1952.

The infant mortality rate has decreased continuously from 115 per 1,000 live births in 1870 to 81 in 1900 and to 29.6 in 1948. The decline has been most marked among infants between 2 and 12 months of age, and less among infants under 1 month of age. Neonatal death has remained almost stationary during the period from 1900 to 1940. During the last eight years,

however, the neonatal mortality rate has shown a decreasing trend also. The importance of further efforts to combat neonatal mortality by means of better care of all pregnant women is stressed, with special regard to adequate nutrition and improved hygiene in general and adequate facilities for treatment of prematurity in maternity hospitals.

WALLGREN, Stockholm, Sweden.

Prematurity and Congenital Deformities

FETAL MORTALITY IN CESAREAN SECTION. H. R. LITCHFIELD, S. D. STERNBERG, J. HALPERIN, and R. TURIN, J. A. M. A. **151**:783 (March 7) 1953.

The higher infant mortality in Caesarean section, even in the elected group, is discussed, and the following recommendations are made: (1) slow release of amniotic fluid upon opening the uterus; (2) transfusion of the infant with placental blood before clamping the cord; (3) gentle suctioning of the oropharynx; (4) insufflation with oxygen when necessary; (5) aspiration of the stomach; (6) placing the infant in the incubator at Trendelenburg position 10 degrees down, and (7) giving vitamin K, pencillin, oxygen and withholding all feedings for 24 hours.

KIMBALL, Evanston, Ill.

STUDIES OF TERRAMYCIN IN PREMATURE INFANTS. FISCHEL J. COODIN, Pediatrics **12**:652 (Dec.) 1953.

In a study of 57 treated premature infants and 56 control premature infants, the daily administration of 25 mg. of oxytetracycline (Terramycin) in the formula failed to alter the rate of weight gain. Changes in the bacterial flora of throat and stool as a result of the oxytetracycline administration were studied and their possible implications discussed.

FROM THE AUTHOR'S SUMMARY.

Newborn

URINARY WATER EXCRETION AND NEUROHYPOPHYSIAL FUNCTION IN FULL TERM AND PREMATURE INFANTS SHORTLY AFTER BIRTH. ROSE G. AMES, Pediatrics **12**:272 (Sept.) 1953.

In infants studied in the first month of life there was a gradual development of the ability to excrete excess water in a short period of time. When a water load was given according to body weight, orally or intravenously, no diuresis was observed in infants under 3 days of age. In comparison, all persons tested over 3 days of age responded with a definite increase in water excretion. As early as 2 weeks of age and in all infants over 1 month of age, the entire water load of 3 to 5% of their body weight was excreted in a three-hour period following the administration of fluid. No difference in the diuretic response to a water load was apparent in full-term and premature infants of comparable postpartum age.

Antidiuretic hormone, whether produced endogenously following thirst, excitation, or pain, or injected in the form of exogenous antidiuretic principle, caused a decrease in urine output only in infants who received a water load and who were responding to it with a diuresis.

When diuresis followed a water load, the degree of the renal response to antidiuretic hormone could not be compared in the various age groups studied, because of the inability to control a sudden release of endogenous hormone provoked by excitatory stimuli.

The hormone was detectable in the urines of infants under three days of age after fluid deprivation; this is assumed to be evidence of a functioning neurohypophysis.

FROM THE AUTHOR'S SUMMARY.

THE PATHOGENESIS OF HEMORRHAGES OF THE NEWBORN. M. BERNARDI, E. GRASSO, S. NASSO, A. VERGA, and R. ALBANESI, Lattante **24**:219 (April) 1953.

At least 3 and usually more of 11 different tests were made with 339 newborn infants in an endeavor to reveal the existence of a basal condition which could explain the hemorrhagic tendency found in newborn infants. Normal values were obtained except that (1) the prothrombin time is prolonged between the second and the fourth day of life, (2) the residual

prothrombin is considerably diminished during the first week of life, and (3) the fibrinolytic and the heparin activity of the blood are increased in the first week of life. The stress a newborn infant undergoes at birth, as emphasized by Selye, can explain these changes and the hemorrhagic tendency. It must be recognized that inherent pathology in any individual infant may be the cause or may aggravate the stress effect.

HIGGINS, Boston.

UNILATERAL SKIN VESSEL CRISIS IN THE NEWBORN. GILLIS HERLITZ, Acta pædiat. **42**:506 (Nov.) 1953.

The causal mechanism of two types of cerebral birth injury—hemorrhages and the hypoxemic ganglion-cell lesions—is discussed in connection with four cases of unilateral skin vessel crises in infants during the first months of life. At birth and during the initial postnatal period all the infants had been in a state of universal cyanosis, but, with one exception, they did not present any signs of a brain lesion. Within a period of 4 to 28 days after birth sudden attacks of severe pallor or redness occurred all over one-half of the body with sharp delimitation in the median line. The author has not been able to find similar observations in the literature. It is thought to be due to minor brain lesions occurring during delivery located in or near the suprasegmental autonomic centers in the medulla or the hypothalamus.

FROM THE AUTHOR'S SUMMARY.

CHILDREN OF DIABETIC MOTHERS: ELECTROCARDIOGRAPHIC STUDIES IN THE NEWBORN. STIG-IVAR BJORKLUND, Acta pædiat. **42**:526 (Nov.) 1593.

In the belief that the adrenal hyperplasia often seen in the children of diabetic mothers is associated with hyperfunction of the adrenal glands and that it may disturb the electrolyte balance and thereby also disturb cardiac function, 15 children of diabetic mothers were examined. The investigation included an analysis of serial electrocardiograms traced in the neonatal period. In four cases the serum potassium was also determined. Abnormal electrocardiograms were seen in 11 cases. The electrocardiographic changes resembled those seen in hypopotassemia. The cause of this disturbance of the electrolyte metabolism is discussed.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

THE TREATMENT OF ENTEROBIASIS (OXYURIASIS): THE NEED FOR A SPECIAL SLEEPING GARMENT. B. H. KEAN, J. Pediat. **43**:47 (July) 1953.

The author states that the adult pinworm lives probably no more than eight weeks, and if reinfestation does not occur, the parasite will be eliminated without medical treatment.

As any practitioner knows, the treatment of pinworm is a difficult problem. Kean suggests that treatment should be directed to the prevention of reinfestation by mechanical means and to the reduction of the worm burden and egg production below the biologic level necessary to perpetuate the disease.

He suggests that these objectives may be attained by (1) the use of a "seal-in" sleeping garment to prevent anal contamination of the fingers, (2) morning showers to wash away eggs deposited in the perianal region during the night, (3) drugs in sequence, for example, gentian violet for 7 days followed by oxytetracycline (Terramycin) for 3 days, followed by parabenzylphenylcarbamate (Diphenan for 10 days, followed by hexylresorcinol for 1 day, (4) chlorcyclizine (Perazil) as an anal ointment, (5) biweekly enemas, (6) the usual auxiliary methods of washing hands after the toilet, cleansing the toilet seat once daily, and vacuuming and airing the house once weekly, and (7) simultaneous treatment of siblings and playmates.

MACDONALD, Pittsburgh.

AUREOMYCIN IN THE PROPHYLAXIS OF RHEUMATIC FEVER. LEON V. MCVAY JR. and DOUGLAS H. SPRUNT, New England J. Med. **249**:387 (Sept.) 1953.

The authors studied the effect of the administration of 250 mg. of chlortetracycline (Aureomycin) twice daily on the prophylaxis of rheumatic fever.

Thirty-five patients from a low economic level were included, 23 of whom received the chlortetracycline and 12 of whom were given a placebo. All the subjects had had a rheumatic attack at least once.

The conclusions were that chlortetracycline appears to be an effective prophylactic agent in rheumatic fever. This antibiotic may be less dangerous for prolonged use than either sulfadiazine or penicillin. Extensive studies revealed no evidence of the development of significant resistance by Group-A beta-hemolytic streptococci to prolonged chlortetracycline therapy. This antibiotic should be of great value in cases in which patients are unable to tolerate either sulfonamides or penicillin.

WHEELOCK, Denver.

Chronic Infectious Diseases

TOXOPLASMOSIS: II. INTRA-UTERINE INFECTION IN DOGS, PREMATURE BIRTH, AND PRESENCE OF ORGANISMS IN MILK. D. M. CHAMBERLAIN, F. L. DOCTON, and C. R. COLE, Proc. Soc. Exper. Biol. & Med. **82**:198 (Feb.) 1953.

Five healthy virgin bitches 1.5 to 2 years of age and a 3-year-old male dog were isolated for three weeks and given an inocula consisting of peritoneal exudate and/or a pooled emulsion of brain heart, lungs, liver, spleen, and kidneys from toxoplasma-infected mice. One received toxoplasma of human origin, three of canine origin, and one from swine. After an incubation period of 3 to 5 days, all except one manifested visible signs of disease. Toxoplasmosis was isolated from 23 to 28 pups born. In utero transmission of toxoplasmosis was demonstrated by isolation of toxoplasma from each of eight pups (born of four bitches) which were collected aseptically and killed at the time they emerged from the birth canal. There was isolation of organisms from the placenta and allantoic fluid. A mammary-gland emulsion from one animal and samples of milk collected aseptically from four lactating infected bitches each revealed toxoplasma.

HANSEN, Galveston, Texas.

HYDRAZINE ISONICOTINIC ACID DERIVATIVES IN TUBERCULAR MENINGITIS. N. I. SPYROPOULOS, I. D. MAROUDAS, and G. BECHRAKIS, Presse méd. **61**:464 (March) 1953.

The authors had previously reported on the results of their trials with hydrazine isonicotinic acid derivatives in pulmonary tuberculosis. The present paper deals with their personal experience with the same treatment in five cases of tubercular meningitis.

The oral dose was either 10 mg. daily per kilogram of body weight for a course of 10 to 20 days or 7 mg. daily per kilogram of body weight for a course of 30 days.

The following are the main observations as made possible from this short experience:

Clinical phenomena were improved after 10 days of treatment, particularly as regards sleepiness and general condition.

Albumin of the cerebrospinal fluid increased during the first and second month of treatment, then regressed.

Sedimentation rate did not correspond with the severity of the disease.

On conclusion, the average dose (5 mg. per kilogram of body weight) of the compound is sufficient to obtain an adequate concentration of the drug in the cerebrospinal fluid, with no toxic side-effect, and to yield more satisfactory results than with the use of streptomycin.

FROM THE AUTHORS' SUMMARY.

A STUDY OF ELECTROENCEPHALOGRAMS IN CHILDREN'S TUBERCULOUS MENINGITIS. PROGNOSTIC VALUE. P. LAGET, C. BACH, C. ALUFI, and R. A. MARQUEZY, Presse méd. Supp. 47, p. 984 (July 8) 1953.

This study is based on 408 tracings from 59 children affected with tuberculous meningitis and followed up during the whole course of the disease by means of monthly tracings.

Usual modifications in the tracings consisted in appearance of slow waves, but other aspects could be observed such as very flat tracings, slow peaks, and rapid rhythms of high voltage.

The electrical abnormalities were usually diffuse and most frequently with a posterior predominancy, which location did not seem to be of particular significance. Asymmetry in the tracings was frequently seen, but oftenest with no clinical correspondency.

Prognostic value of the initial tracing seemed remarkable; in 75% of the fatal forms the initial tracing was much altered, whereas in the curable forms it was only altered in 35% of the cases. The authors think this alteration of the initial tracing to be of more prognostic value than consciousness disorders.

As a rule, the electroencephalographic evolution was parallel to the clinical course, but the electrical improvement usually appeared only after the clinical improvement.

Slight abnormalities in the tracings lasted, in half the cases for a long time after clinical cure and discontinuance of treatment, but usually disappeared in the long run.

The authors think it presumptuous to infer a topography of the lesions from the morphology and location of the electrical changes.

FROM THE AUTHORS' SUMMARY.

LIVER TUBERCULOSIS IN CHILDHOOD. EUGENE STRANSKY, ELEONORA P. DACANAY, PERPETUA S. LACSON, and AMBROSIO REYES, Ann. pædiat. **181**:329 (Dec.) 1953.

Four cases of tuberculosis of the liver are presented. In three cases there are multiple small calcified spots in the markedly enlarged liver. These three children are all 11 to 12 years old. The clinical symptoms suggest either liver cirrhosis or malignant hepatoma. The x-ray findings in the liver and the evident involvement of other organs in the tuberculous process, as well as the liver-aspiration biopsy, may be of help in the differential diagnosis. There is no jaundice, and the liver functions do not seem to be markedly impaired. In long-standing cases, increase of the serum protein with marked increase of the serum globulin level and inversed albumin/globulin ratio are observed. There is marked arrest of body development in the observed cases. A fourth case is presented in a 7-year-old child with solitary tubercles of the liver with typical x-ray findings. It is believed that tuberculosis of the liver is not rare; the clinical symptoms are very suggestive, while the radiological symptoms are characteristic. The therapy is the same as in any other tuberculous disease.

FROM THE AUTHORS' SUMMARY.

THE SURGICAL TREATMENT OF TUBERCULOUS CERVICAL LYMPH GLANDS. E. KAISER, F. JAKOB, and H. WISSLER, Schweiz. med. Wchnschr. **83**:207 (Feb. 28) 1953.

The tuberculous cervical glands of 221 patients observed at a sanitarium *pro juventute* were removed. Later controls after an interval of 3 months to 10 years could be obtained in 167 patients. Small recurrent lymphomas within the region of the scar without formation of fistula were seen in nine cases. The cosmetic result was unsatisfactory in 3%. Tonsillectomy had no influence on the frequency of recurrence.

AMBERG, Rochester, Minn.

KIND AND FORM OF THE BCG SKIN LESIONS. H. WESPI, Schweiz. med. Wchnschr. **83**:260 (March 14) 1953.

The cutaneous lesions following the intracutaneous vaccination with BCG are described, with special reference to the ulceration at the place of vaccination after about six to eight weeks. This ulcer heals slowly and should never be excised, as has been done. The histology is that of tuberculosis colliquativa cutis. The success of the vaccination, that is, the change of a negative cutaneous tuberculin reaction to a positive one, is more certain with the occurrence of these ulcers. Colored illustrations of the lesion observed in young adults are given.

AMBERG, Rochester, Minn.

KIND AND FORM OF THE BCG SKIN LESION. F. PUNTIGAM and K. BERGER, Schweiz. med. Wchnschr. **83**:559 (June 13) 1953.

Children who had received BCG intracutaneously were tested with intracutaneous injections of old tuberculin. When these persons again received BCG intracutaneously, they responded differently from those receiving BCG the first time. As early as three days after the second BCG, redness of the place of injection occurred and an infiltration of 3 mm. to 5 mm. rapidly increased and ulcerated superficially. These ulcerations were observed in about 93% of these

cases as compared with about 12% of those vaccinated for the first time. The revaccinated cases did not respond with swelling of regional lymph glands. In full accord with Wespi, it was demanded that the physicians should be familiar with the skin lesions concequent to BCG injections to avoid unnecessary surgical interference.

AMBERG, Rochester, Minn.

INVESTIGATION OF THE PROBLEM OF GENERAL REACTIONS AFTER BCG VACCINATION. H. WISSLER and J. TUCKOVA, Schweiz. med. Wchnschr. **83**:1059 (Oct. 31) 1953.

The examination of 124 BCG-vaccinated children was compared with the examination of 117 nonvaccinated tuberculin-negative children. No elevations of body temperature were observed in the vaccinated group referable to the vaccination. Roentgen examination before and after vaccination in 54 children did not reveal noteworthy changes in the hilus of the lungs. The results confirm the clinical observations and routine x-ray examinations of about 200 vaccinated children that general disturbances after vaccination are not any more frequent than without it.

AMBERG, Rochester, Minn.

OUR FIRST YEAR'S EXPERIENCE WITH ISONIAZID IN THE CHILDREN'S HOSPITAL OF BRESCIA AND THE CHILDREN'S SANATORIUM OF VALLEDRANE. A. PAGANI-CESA and A. BORTA, Clin. pediat. **35**:536 (Aug.) 1953.

Two hundred eighty-two children with tuberculosis were treated by isoniazid, either with or without streptomycin. The general health and appetite of the children were observed to improve when the drug was given; there was also an increase in body weight, even when there was but little change noted by x-ray examinations. The isoniazid was well tolerated by babies in amounts of 10 mg. per kilogram of body weight daily in four divided doses.

The isoniazid proved especially useful in those cases where the tubercle bacilli were streptomycin-resistant or there was an idiosyncrasy to streptomycin.

Isoniazid did not prove so efficacious in the glandular as in the more diffuse types of tuberculosis.

HIGGINS, Boston.

THE CLINICAL COURSE OF TUBERCULOUS MENINGITIS TREATED BY ISONIAZID INTRASPINALLY, ORALLY, AND PARENTERALLY. G. C. ABBA and C. PEREGO, Clin. pediat. **35**:551 (Aug.) 1953.

Since isoniazid has been given to supplement streptomycin in the treatment of children with tuberculous meningitis in the Children's Hospital at Brescia, the percentage of cures has risen from 37 to 83%.

HIGGINS, Boston.

TREATMENT OF TUBERCULOUS MENINGOENCEPHALITIS BY THE USE OF ORAL ISONIAZID AND INTRAMUSCULAR STREPTOMYCIN. MANUEL SUAREZ Rev. españ. pediat. **8**:689 (Sept.-Oct.) 1952.

This is a presentation of seven cases with excellent results obtained in the use of oral isoniazid and streptomycin intramuscularly.

The author feels that intrathecal medication is no longer necessary.

The details concerning the spinal fluid changes, laboratory findings, and clinical improvement are included.

Most of the children showed rapid improvement with clinical recovery complete in from six weeks to two months of treatment. Children with longstanding history of the disease needed treatment over a period of two years.

The details of medication and treatment are given.

ALLEN, Santa Fe, N. Mex.

ON THE ETIOLOGY OF TUBERCULOUS MENINGITIS. ROBERT DEBRE and H. E. BRISSAND, Rev. españ. pediat. **9**:649 (July-Aug.) 1953.

The authors summarize the findings at the Streptomycin-Therapy Center at the clinic in the Hospital for Children in Paris.

The etiology is studied from the standpoint of contacts. Usually the patients have early massive exposure to the tubercle bacillus, usually from close family contact. Many show that the tubercle is resistant to streptomycin; the bacilli get into the bronchial tree first. Infection by bovine tuberculosis through the digestive tract is rare.

The question of reinfection is discussed. In the opinion of the author figures did not show that BCG helped prevent the infection in children seen at this hospital.

Most of the cases were under 5 years of age; eight had a history of trauma to the head; the effect of heredity cannot be properly evaluated in these cases, as few had been isolated from affected parents.

ALLEN, Santa Fe, N. Mex.

Diseases of Blood, Heart and Blood Vessels, and Spleen

DIAGNOSIS AND TREATMENT OF PATENT DUCTUS ARTERIOSUS IN INFANCY. PAUL ADAMS JR., FORREST H. ADAMS, RICHARD L. VARCO, J. FRANCIS DAMMANN JR. and WILLIAM H. MULLER, Pediatrics **12**:664 (Dec.) 1953.

A large patent ductus arteriosus can produce obvious cardiac difficulty and death in infancy.

The diagnosis of a patent ductus arteriosus in infancy can be difficult in the absence of a continuous murmur. In such instances special studies, such as cardiac catheterization or retrograde aortography should be performed to establish the diagnosis.

Surgical closure of the patent ductus arteriosus can and should be performed in those infants with symptoms and findings of cardiac difficulty—dyspnea, cardiomegaly, murmur, and marked growth failure.

Data have been presented on 16 infants with patent ductus arteriosus in whom surgical closure of the patent ductus arteriosus was deemed necessary before 18 months of age.

Of the 16 infants, one died during surgery (6% mortality rate) and the remaining showed marked improvement following surgery. Postoperative rate of growth was variable in patients followed one year or less and consistently improved in those followed one and one-half years or more.

FROM THE AUTHORS' SUMMARY.

ABSENCE OF THE INFERIOR VENA CAVA. DANIEL F. DOWNING, Pediatrics **12**:675 (Dec.) 1953.

Two patients with absence of the inferior vena cava are presented. Both were shown to have associated cardiovascular anomalies. A roentgen sign which may be of diagnostic aid is described.

FROM THE AUTHOR'S SUMMARY.

RELATIONSHIP BETWEEN THE HEMOGRAM OF THE INFANT AND THAT OF THE MOTHER DURING PREGNANCY. CALVIN W. WOODRUFF and EDWIN B. BRIDGEFORTH, Pediatrics **12**:681 (Dec.) 1953.

In the absence of maternal iron deficiency, maternal hemoglobin concentration is not related to the development of iron-deficiency anemia in infancy.

FROM THE AUTHORS' SUMMARY.

SEROLOGIC FINDINGS IN EXSANGUINATION TRANSFUSION. H. ZWIRN, Ann. pædiat. **181**:343 (Dec.) 1953.

The possibility exists that, after exsanguination transfusion of 500 cc., the remaining Rh-positive blood corpuscles, the persistent antibodies, and the bilirubin may exert an injurious influence on the tissue. The aim of our therapy must therefore be to reduce these substances to a minimum. Diamond's and Wiener's better results with larger transfusion amounts are probably due to a further reduction of antibodies and bilirubin in the child's organism, an assumption which should be confirmed by special investigations. These better results and our serological findings in exsanguination transfusion in 31 cases show the inadequacy of transfusing less than 700 cc. of blood.

FROM THE AUTHOR'S SUMMARY.

AGRANULOCYTOSIS AFTER THE USE OF ISONIAZID ACID HYDRAZIDE. E. NASSUA and A. BORTNIK, Ann. pædiat. **181**:371 (Dec.) 1953.

A patient with tuberculous peritonitis was given six gm. of isoniazid in the course of 60 days. At the end of this time she developed agranulocytosis with sore throat, which cleared up quickly when the medication was stopped. It is improbable that the agranulocytosis was due to *p*-aminosalicylic acid, because reintroduction of *p*-aminosalicylic acid had no influence on the leucocytes and because agranulocytosis may only be caused by *p*-aminosalicylic acid when the quantities of the drug are much larger, so large in fact that severe toxic liver damage would ensue. Isoniazid is not stored in the body, but is excreted very quickly. This behavior explains the rapid improvement of the blood picture after cessation of treatment. The possibility that isoniazid may be in rare cases the cause of agranulocytosis necessitates control of the blood during this treatment.

FROM THE AUTHORS' SUMMARY.

SICKLE CELL ANEMIA IN GREECE. C. CHOREMIS, N. ZERVOS, B. CONSTANTINIDES, L. ZANNOS and S. SKLAVOUNOU, Schweiz. med. Wchnschr. **82**:709 (July 5) 1952.

Of 1,016 inhabitants of a small city in Greece, 159 presented sickling. Previously reported cases of sickle cell anemia in 15 children and their parents were not included. The age group up to 15 years participated with 46.4%. The total incidence of sickling, with about 15.5%, exceeds that of American Negroes given as 8%. Various etiological factors are discussed. Some importance is attributed to such factors as undernourishment, malaria, intermarriages, and possibly climatological factors. These factors also may be of significance in Cooley's anemia, although sickle cell anemia and Cooley's anemia are regarded as separate disease entities. Hereditary factors are also discussed.

AMBERG, Rochester, Minn.

THE BEHAVIOR OF CULTURES IN VITRO OF BONE-MARROW CELLS FROM CHILDREN BEING TREATED WITH CORTISONE. BIANCA RONDININI, Clin. pediat. **35**:582 (Aug.) 1953.

Cultures of bone-marrow cells from two children with leukemia before and during cortisone treatment failed to reveal any fibroblastic evolution of surviving leukemic cells. The suggestion is made that any cytolytic action of cortisone is but temporary because of an increased tissue resistance to the hormone.

HIGGINS, Boston.

ACUTE MALIGNANT HISTIOCYTIC RETICULOSIS IN AN INFANT. M. BELLONI, Pediatria **61**:688 (Sept.) 1953.

A nine-month-old baby girl over a period of four months had gradually developed purpuric papules with crusting and desquamation over her entire trunk, irregular bouts of fever, anemia, enlarged tonsils, lymph nodes, spleen and liver, gingivitis, and annoying coughing. The smears of the bone marrow revealed no abnormal cells, and the peripheral blood showed a low red cell count, some erythroblasts, a slight leucocytosis, and a normal platelet count. Thinness of the bones of the skull and the presence of nodules in the lung fields were noted on x-ray examination. Histological examination of the skin revealed many histiocytes. Antibiotics proved of no clinical benefit. The child died of a rapidly progressive bronchopneumonia. There was no family history of any similar condition. A diagnosis of Abt-Letterer-Siwe disease was made.

HIGGINS, Boston.

HAND-SCHÜLLER-CHRISTIAN SYNDROME. A. MALLARDI, Pediatria **61**:801 (Sept.) 1953.

A case report with autopsy findings is presented of a 7-year-old girl who had the typical findings of xanthomatosis (Hand-Schüller-Christian syndrome).

HIGGINS, Boston.

TWO CASES OF DEXTROCARDIA IN INFANTS. MAXIMILLIANO MARTINEZ SANCHEZ, Acta pediat. españ. **11**:353-363 (March) 1953.

The author presents the case histories of two infants with situs inversus viscerum totalis. One was found in the examination for a mild upper respiratory infection; the other had developed a lung abcess before coming to the author's attention. Both survived.

In a careful family history the author was impressed by the fact that both mothers had had several spontaneous abortions before the patient was born. There was no evidence of syphilis. The author felt that germ plasm defect might be a factor. Both fathers were somewhat older than usual, as were the mothers. In the first case reported there were two uncles on the mother's side who, although quite healthy, presented the same anomaly. ALLEN, Santa Fe, N. Mex.

PATENT DUCTUS ARTERIOSUS: CLINICAL AND SURGICAL EXPERIENCES. ENRIQUE GARCIA and FRANCISCO JACA CRENDE, Acta pediat. españ. **11**:479-507 (May) 1953.

The authors review the literature and give details of their experiences in the study of 89 cases with 56 operations at the Central Red Cross Hospital in Madrid.

The study includes a review of the embryology and the physiology of circulation in the fetus and in the adult in cases of patent ductus arteriosus, and the diagnosis, including auscultatory, electrocardiographic, radiological, and angiocardiographic techniques, as well as catheterization.

They discuss the importance of aximetric studies and describe the details of the surgical technique. The reasons for decision for operation are discussed fully. The need for the cardiologist to follow frequently and minutely the progress of a patient with ductus arteriosus is emphasized. Although the age of the patient is an important factor in this decision, the clinical picture is more important. The operation is simpler, in the authors' experience, if it is performed between the ages of 3 and 12 years. There were two fatalities in the 56 cases, the other 54 have responded very well to surgery. The eventuality of the patient remaining an invalid of myocardial cicatrization must always be kept in mind. The possibility of other anomalies must be remembered. Rheumatic mitral stenosis is, however, no contraindication.

In cases of doubt the manometer and the aximeter should have the last word, since cases which show a manifest or even an occasional pulmonary hypertension should not have the operation.

ALLEN, Santa Fe, N. Mex.

Diseases of Nose, Throat, and Ear

THE RESPONSE OF PROFOUNDLY DEAF CHILDREN TO AUDITORY TRAINING. CLARENCE V. HUDGINS, J. Speech & Hearing Disorders **18**:273 (Sept.) 1953.

Hudgins presents a progress report on an experimental program designed to study the effectiveness of auditory training for profoundly deaf pupils in order to show to what extent the small remnant of hearing in profoundly deaf children may be trained and employed when the very best acoustical equipment is available. The present study concerns a group of 8 profoundly deaf children compared with 12 control cases. Such children are definitely benefited by the use of hearing aids, which are capable of amplifying sound well above their thresholds, in speech perception, general educational achievement, and, to a lesser degree, speech intelligibility. High-powered equipment in a relatively nonreverberant room, capable of presenting undistorted speech signals at levels near the threshold of pain and with a power-limiting device that protects the ear from discomfort or acoustic trauma is necessary.

PALMER, Wichita, Kan.

HEARING IMPAIRMENTS IN CHILDREN. CHARLES E. KINNEY, Laryngoscope **63**:220 (March) 1953.

Studies of hearing loss in children reveal that the conductive lesions are twice as prevalent as the preceptive ones. Preventable otitis media causes most of these hearing impairments. Measles probably produces more deafness than has been thought. Middle-ear effusion is on the increase, both relatively and actually.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

INDICATIONS FOR TONSILLECTOMY AND ADENOIDECTOMY IN CHILDREN. G. O. PROUD, Laryngoscope **63**:262 (March) 1953.

Although the tonsillectomy and adenoidectomy operations are perhaps the most abused in surgery, there are still definite indications for them. Adenoidectomy may often be done without removing the tonsils. Indications for adenoidectomy are mouth breathing, adenoid facies (rare),

recurrent otitis media or secretory otitis, and hearing loss due to tubal obstruction. Surprisingly enough, adenoidectomy relieves the obstruction in many cases of vasomotor rhinitis.

There are certain indications for tonsillectomy. Some are quinsy, recurrent Vincent's angina or diphtheria of the tonsil, and frequent tonsillitis. The best age for tonsillectomy is between 4 and 12 years.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

ENDOTRACHEAL ANESTHESIA IN CHILDREN. JOHN J. HOCHFILZER, Laryngoscope **63**:395 (May) 1953.

Hochfilzer stresses the value of endotracheal anesthesia, especially for tonsil and adenoid surgery. He asserts that if the tube is inserted properly there will be no complications. In over 500 cases, the only complications were 2 cases of hoarseness postoperatively. With intertracheal anesthesia the airway is kept open, preventing anoxemia, so commonly observed during tonsillectomy, and the danger of aspiration and asphyxia is eliminated. Hochfilzer feels that physicians should learn this method and use it routinely.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

ACUTE FEBRILE PETECHIAL OROPHARYNGITIS: PRELIMINARY REPORT. MORTON B. WALLACH, SHIRLEY SCHMONES, and SIDNEY W. BEREZIN, New York J. Med. **63**:1553 (July 1) 1953.

What the authors call "an extremely contagious outbreak of acute febrile petechial oropharyngitis" was observed by them during July, 1952. One hundred cases have been collected, all "extremely contagious," in children only; no cases have been observed in adults. Incubation is from 24 to 48 hours, when small vesicles appear on the hard and soft palate and pharynx. The temperature rises to 103 F., sometimes as high as 106 F. The child clutches his throat and complains bitterly of a headache and pains throughout his body; especially in the muscles and tarsal bones. The discrete vesicles coalesce, forming large hemorrhagic blotches. The cervical glands are enlarged and tender, but prostration is slight. The temperature decreases by crisis, but a sore mouth persists, with an occasional pustule on a tonsil. This is a brief self-limited disease making it unnecessary for the patient to be hospitalized. The patient does not respond to penicillin when it is administered but does respond to oxytetracycline (Terramycin) when the disease is in the prodromal stage. Laboratory and other work-up tests have not been sufficiently carried out as yet because of the short duration of the disease and the very acute symptoms, although the "course is benign."

ABSTRACTOR'S COMMENT: This sounds like a viral infection which is rather quickly overcome by the defense mechanism of the body. This latter element is of particular interest and value if it can be worked out, for there are so many viruses which overwhelm the body against all defenses, natural and therapeutic.

I. W. VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura, and Mediastinum

THE RELATIVE EFFICACY OF ERYTHROMYCIN (ILOTYCIN) AND OF PENICILLIN IN THE TREATMENT OF PNEUMOCOCCAL LOBAR PNEUMONIA. ROBERT AUSTRIAN and ROBERT ROSENBLUM, Am. J. Med. Sc. **226**:487 (Nov.) 1953.

Fifty patients with proved pneumococcal lobar pneumonia were studied at Kings County Hospital in Brooklyn. Twenty-four patients were treated with erythromycin and 26 patients with infections of comparable severity were treated with intramuscular aqueous penicillin. The results obtained were similar with these two antibacterial agents. The authors suggest that erythromycin be reserved as an alternate form of therapy for pneumococcal lobar pneumonia.

SUTTON, Evanston, Ill.

AGENESIS OF THE LUNG WITH VASCULAR COMPRESSION OF THE TRACHEOBRONCHIAL TREE. HERBERT C. MAIER and WILBUR J. GOULD, J. Pediat. **43**:38 (July) 1953.

Maier and Gould report a case of agenesis of one lung with respiratory difficulty and death caused by vascular compression of the airway. An anomalous pulmonary artery and the position of the aorta were responsible for the tracheal narrowing. The vascular compression was not obvious at autopsy since after death the large arteries were no longer full and tense. In this case, the vascular compression was obvious at the time of exploratory thoracotomy.

MACDONALD, Pittsburgh.

STAPHYLOCOCCAL PNEUMONIA, AND EMPYEMA. ABRAM KANOF, BERNARD EPSTEIN, BENJAMIN KRAMER and IRVING MAUSS, Pediatrics **11**:385 (April) 1953.

Forty-one cases of staphylococcal pneumonia, treated with sulfonamides, sulfonamides plus penicillin, and with chlortetracycline (Aureomycin) plus penicillin, are described. Since characteristic bacteriologic findings are now uncommon, diagnosis of this condition depends on the presence of a typical clinical and roentgenologic picture, herein described.

The mortality rate with sulfonamide treatment alone was 50%. The mortality rate in cases treated with sulfonamides and penicillin was 25%. With the introduction of chlortetracycline none of 12 consecutive cases in this series died.

Empyema treated with sulfonamides and penicillin often cleared with repeated aspiration alone or aspiration followed by instillation of penicillin into the pleural cavity. Cases of empyema treated with chlortetracycline plus penicillin seldom required paracentesis.

FROM THE AUTHORS' SUMMARY.

INTERSTITIAL "PLASMA CELL" PNEUMONIA OF PREMATURE AND YOUNG INFANTS. WILLIAM C. DEAMER and HANS U. ZOLLINGER, Pediatrics **12**:11 (July) 1953.

An unusual type of infantile pneumonia occurs frequently in certain European countries but thus far is undescribed in the American literature. It is remarkable clinically in being almost asymptomatic until late in its course, in showing a marked predilection for premature or immature infants, and for being confined to the age period of six weeks to four months.

Pathologically, it is remarkable for a diffuse interstitial pulmonary infiltration by mononuclear cells which, for the most part, closely resemble plasma cells. An alveolar exudate is also present.

About 22% of recognized cases die of asphyxia. In these cases death appears to be predominately due to asphyxia.

The most commonly held opinion, in which we concur, is that the disease is infectious and probably of viral origin, but as yet there has not been a convincing demonstration of the etiologic agent. Up to the present time no effective therapeutic agent has been found.

FROM THE AUTHORS' SUMMARY.

DIAGNOSIS OF SO-CALLED PRIMARY ATYPICAL PNEUMONIA IN CHILDHOOD. F. BUSER, Schweiz. med. Wchnschr. **83**:822 (Aug.) 1953.

Buser reports five illustrative cases in which diagnoses of primary atypical pneumonia were made in children 7 to 11 years of age. As special features, Buser mentions resistance to sulfonamides and penicillin and the cold agglutination. This cold agglutination decreases in the third to fourth week of illness, while, for instance, in cases of tuberculosis the titer remains high for a longer period of time. Another feature is the discrepancy between clinical symptoms and x-ray examination of the lungs. The differential diagnosis from bacterial pneumonia, aspiration pneumonia, tuberculous lung lesions, and Q fever is discussed as well as differential diagnosis from etiologically better-known virus diseases, such as ornithosis, psittacosis, influenza A and B, and meningopneumonia.

AMBERG, Rochester, Minn.

THE ESTABLISHING OF A PATHOLOGICAL DIAGNOSIS, WHEN THERE IS A LABILE INFILTRATION IN THE LUNGS. L. MATTEUCCI, Clin. pediat. **35**:420 (June) 1953.

The importance and reliability of the tuberculin test are discussed, when one must differentiate between a tuberculous and a nontuberculous pulmonary disease.

HIGGINS, Boston.

THE ABSORPTION BY THE LUNGS OF A NEW WATER-SOLUBLE DERIVATIVE OF CHLORAMPHENICOL. M. MALASPINA, Minerva pediat. **5**:627 (Aug. 15) 1953.

The succinate of chloramphenicol was used in tests with normal children. In some observations a mask was used, the air being inhaled through a water solution of the drug; in other observations the child was placed in a small room (eight cubic meters), the solution being atomized into the room. This latter method resulted in a higher blood level and a greater urinary excretion of the drug.

HIGGINS, Boston.

LEUKOSARCOMA OF STERNBERG ARISING IN THE PLEURA OF A CHILD. CARLOS MONTALVO SOTOLONGO, Rev. cubana pediat. **25**:231 (April) 1953.

The author reports the case of a 3-year-old boy with a pleural tumor. Biopsy of an axillary lymph node showed the picture of Hodgkin's disease. The patient developed the peripheral blood picture of leukemia and died.

NELSON, San Francisco.

A CONTRIBUTION TO THE ETIOLOGY OF ACUTE INTERSTITIAL PLASMACELLULAR PNEUMONIA. H. MORITSCH, Wien. klin. Wchnschr. **65**:280 (April 10) 1953.

In a boy 9 weeks of age a diagnosis of acute interstitial plasmacellular pneumonia was made. The sputum was injected in mice without demonstration of virus. On postmortem examination, swabs were taken from the lung. In these, as well as in sections of the alveolar epithelium, Pneumocystis carinii was found.

AMBERG, Rochester, Minn.

A CASE OF TRUE ABERRANT LOBE OF THE LUNG. HANS BRUCK, Wien. klin. Wchnschr. **65**:304 (March 27) 1953.

A girl 21 years of age was operated upon for a diaphragmatic hernia which had been diagnosed at the age of 10 years. At the operation, a circumscribed relaxation of the diaphragm was found intimately connected with a mass which was removed successfully, and the assumption of a supernumerary lobe of the lung was verified on histological examination.

AMBERG, Rochester, Minn.

A CLINICAL STUDY OF RESPIRATORY DISEASES WITH REFERENCE TO INFLUENZA. Z. HLOUSKOVA, J. POPELKOVA, and D. SLONIM, Pediat. listy **8**:279, 1953.

The respiratory diseases are surveyed as they were seen at the Second Children's Clinic in Prague between Oct. 1, 1951, and Dec. 8, 1952; 335 patients were examined in detail, and 912 children in the outpatient department for respiratory illness. Of these 78 were cases of rhinopharyngitis, 2 were cases of laryngotracheitis, 76, cases of bronchitis and bronchiolitis, and 154, cases of pneumonia. They were most numerous in the months of January-April. In 4.5% of the cases respiratory disease was the cause of death, 27.1% were admitted in a very serious condition, and 13.1% had an affection of the central nervous system. Virologically confirmed cases of influenza, mainly Type B, constituted 10% of all respiratory diseases. Antibiotics other than penicillin were given to only 28.3% of the cases. The average stay in the hospital was 10 days.

FROM THE AUTHORS' SUMMARY.

ELECTROENCEPHALOGRAPHIC STUDIES OF ASTHMATIC CHILDREN. BORJE HOLMGREN and SVEN KRAEPELIEN, Acta pædiat. **42**:432 (Sept.) 1953.

One hundred children suffering from bronchial asthma, aged 2 to 15 years, without a hereditary predisposition for convulsive diseases and without any convulsive manifestations of their own, were examined with regard to the occurrence of electroencephalographic changes.

Pathological electroencephalograms of different degrees and types occurred in 36 cases. The type of electroencephalographic changes comprised partly a slow dysrhythmia—in about two-thirds of the cases most evident occipitally—partly focal spikes or sharp waves, in three cases, and general wave and spike episodes in another three cases.

The occurrence of an allergic heredity, the duration of the asthma, and the age of onset showed no correlation to the occurrence of electroencephalographic changes. The degree of severity of the asthma seems to have a certain relation to the occurrence of pathological electroencephalograms. During the acute attack of asthma, marked electroencephalographic changes were observed that subsided after the attack.

The facts underlying the electroencephalographic changes and their relation to the allergic condition are discussed.

FROM THE AUTHORS' SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

EMBRYONAL CELL CARCINOMA OF THE LIVER IN INFANCY. A. J. TOMSYKOSKI and R. C. STEVENS, J. Pediat. **43**:309 (Sept.) 1953.

This is rare. This infant presented a right-sided abdominal mass accompanied by anemia and progressive abdominal distention. She was 9 months old. The diagnosis was made at autopsy.

MACDONALD, Pittsburgh.

FOREIGN BODY REMOVAL BY AL-NI-CO MAGNET. JOSEPH L. HANSEN, Northwest Med. **52**:839 (Oct.) 1953.

The author presents a simple and apparently effective aid in encouraging successful passage of metallic foreign bodies. By having the patients swallow a small inexpensive magnet, a bobby pin and a straight pin were coaxed through the intestinal tract without perforation.

DOCTER, Seattle, Wash.

REPAIR OF CLEFT PALATE AND COLUMELIA WITH A TUBED SKIN PEDICLE. J. CRAWFORD, C. E. HORTON, and R. S. OAKLEY, U. S. Armed Forces M. J. **3**:1713 (Nov.) 1952.

Crawford and his associates do not claim originality for their operation but report a case because of its unusual features. A 40-year-old woman had bilateral cleft of the lip and cleft of both the hard and soft palates. She was operated on without complete success at the age of 4 years. When she was 16, a prothesis was fitted. She has only three primary teeth in the premaxilla, and it appears that there was no eruption of teeth elsewhere. When the patient was 37, her front teeth had become eroded by the prosthesis, and an operation was then advised so that it might be discarded. The earlier operations had all been of the routine type of mucoperiosteal flap reconstruction. Lack of success in these attempts led to the trial of a pedicle tube graft. This was begun on the left side of the abdomen, transferred to the left wrist, and then sutured to the edges of the defect in the palate. After 12 operations to prepare the tube, it became infected in the distal portion, causing the loss of half of the pedicle. Some months later the remaining half of the tube, still present on the wrist, was sutured into the palate defect, but this was accidentally pulled loose. Another tube was then constructed on the right side of the abdomen, but the blood supply was not sufficient to prevent necrosis. Up to this point, 12 additional operations had been done without success. A third pedicle was then made on the chest, but before it was ready to use, the patient's husband, who was in the service, was transferred, and the patient was obliged to leave before the procedure was completed. The foregoing had extended over a period of two years and had involved 40 operations. At this point, the patient came under the care of Crawford and his associates. She still carried a 6-in. (15.24-cm.) pedicle on her chest. After Crawford and his associates had reviewed her history, they decided to try to close the posterior third of the palate cleft with the customary mucoperiosteal flap method. This operation was successfully achieved, but there followed a separation of the anterior portion, leaving only ½ cm. of the palate united. To remedy this condition three months later a posterior pharyngeal flap was raised and sutured to the nasal surface of the closed part of the palate. The results were considered good for partial closure of the defect. To compensate for the remaining opening in the palate, a new prosthesis was provided, but the patient was not satisfied with this

as a final measure. A decision was then made to use the tube still on the chest, and this was done. Only a portion of the tube was employed for this detail, and the remaining part was made use of to lengthen the columella and reconstruct the upper lip. After a total of 51 operations, a satisfactory cosmetic outcome had been reached. This report illustrates how many routine procedures may result in failure.

SELTZER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

THE PATHOLOGICAL PHYSIOLOGY, ASSESSMENT AND MANAGEMENT OF "DEHYDRATION" IN ENTERO-COLITIS. HOWARD WILLIAMS, M. J. Australia **2**:203 (Aug. 8) 1953.

Early loss of water, sodium, and chloride from the body in diarrhea should be corrected quickly to prevent circulatory embarrassment and to restore cell-function. If diarrhea persists, serious depletion of sodium and potassium may occur with symptoms of hypopotassemia and dehydration due to sodium depletion. It is essential to assess the patient's condition carefully to determine whether chronic potassium or sodium depletion or both are present. Treatment consists of adequate replacement of both fluids and the necessary electrolytes.

McGUIGAN, Evanston, Ill.

RECENT TRENDS IN THE DIAGNOSIS AND TREATMENT OF CŒLIAC DISEASE. CHARLOTTE M. ANDERSON, M. J. Australia **2**:211 (Aug. 8) 1953.

Recent studies have revealed that the celiac child can tolerate many more foods than previously believed possible. Careful investigation showed that all foods were taken well except for wheat and rye flour. Further study showed that the offending factor was apparently the gluten. It appears that the long-used celiac diet is not needed, and that these children do well on the single elimination of wheat gluten.

The author recommends that until the mode of action of the gluten is determined, dietary restriction be maintained through the growing period of the child, since some patients, at least, became sufferers from idiopathic steatorrhea.

McGUIGAN, Evanston, Ill.

ON THE THEORY OF THE TOXIC CHOLERIFORM CONDITION IN THE INFANT: I. PHYSIO-PATHOLOGIC ASPECTS. J. CATHALA, P. AUZEPY, BERTRAND CLAVEL, and DANIEL GRAVELEAU, Presse méd. Supp. 59, p. 1185 (Sept. 23) 1953.

The terms cholera, athrepsia, and intoxication indicate syndromes, not diseases as defined by a precise infective or toxic etiology. In the authors' view, use of the word toxicosis (although admitted in the international terminology) is inadvisable as it suggests to the public the idea of a disease, probably infectious, due to some agent or homogeneous group of agents, microorganisms or viruses. Toxicosis is not one disease or a group of diseases. It is a condition logically subsequent to those metabolic disturbances forced upon the system, whatever the primary mechanism, by the inadequacy of the functional circulation necessary for the life of the larger viscera, (brain, kidney, etc.) and by the hydroelectrolytic losses. This explains the different aspects assumed by the condition.

The study of the "metabolic disease," being made possible under aseptic conditions, enabled the authors to discover the facts related to toxicosis when it was infectious in origin, as is clinically observed in most cases.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF PERFORATING APPENDICITIS AND SECONDARY PERITONITIS IN CHILDREN. P. KISS, A. KOÓS, and M. CSUKÁSSY, Ann. pædiat. **179**:12 (July) 1952.

In the years 1948 through 1950 the authors operated on 47 cases of perforating appendicitis with secondary peritonitis. Of these, 95.75% were cured. The mortality was 4.25%. The operations on 70.22% of the children were performed late, i. e., after the second day of illness. Of the patients, 14.89% were below the age of 3 years, or in the "dangerous age."

Treatment consisted of operation at the earliest possible time combined with administration of antibiotics, prevention of dehydration, acidosis, thirst, and hunger, maintenances of adequate blood circulation, and supply of vitamins in necessary quantity and range.

The appendix, except in a few very exceptional cases, was looked for and removed during the first operation.

FROM THE AUTHORS' SUMMARY.

THE RADIOLOGICAL APPEARANCE OF THE SMALL INTESTINE DURING THE ABSORPTION OF FOOD. R. PACHIOLI and G. TONIOLO, Clin. pediat. **34**:561 (Sept.) 1952.

The appearance in and the speed of passage through the small intestine of (1) 15 gm. $BaSO_4$ in 30 cc. of water and (2) 7 gm. $BaSO_4$ and 8 gm. mashed carrots in 30 cc. of water were determined radiographically with 20 children from 2 to 20 months of age. The results were subjected to careful statistical analysis and showed the surprising finding that the carrot pap speeded the passage of the barium through the small intestine. The barium shadows were more diffuse (less clumped) when the carrot pap was given. The conclusion is drawn that the benefit of carrots in diarrhea is traceable to other cause than its local action on the instestine.

HIGGINS, Boston.

A PEDUNCULATED FIBROMA OF THE LIVER, PRESUMABLY CONGENITAL. B. FORMIGGINI, Clin. pediat. **35**:295 (May) 1953.

A very emaciated baby boy of 10 months had a rapidly enlarging abdomen, through the wall of which a large hard tumor could be palpated. Just before death, the baby had a high fever, Cheyne-Stokes breathing, and edema of the lower extremities. The clinical diagnosis was a sarcoma of the kidney. At autopsy, a large fibroma was found attached by a pedicle to the lower right base of the liver. In retrospect, since the tumor was not malignant, surgical removal of the tumor should have been attempted.

HIGGINS, Boston.

DIETETIC TREATMENT OF HABITUAL VOMITING. A. MALLARDI, Minerva pediat. **5**:660 (Aug. 15) 1953.

The author has had considerable success in treating infants with habit vomiting by using a formula containing milk enriched by cream to raise the butter fat to 10% or 20%.

HIGGINS, Boston.

GENERALIZED INTESTINAL POLYPOSIS. ALFREDO GANTZ, RAIMUNDO ARIZTIA and ALBERTO GUZMAN, Rev. chilena pediat. **22**:339, 1951.

A case of generalized intestinal polyposis in an 8-year-old girl is presented. The authors review the literature on this subject.

FROM THE AUTHORS' SUMMARY.

USE OF THE LABORATORY AND OTHER SERVICES ANCILLARY TO THE CLINIC IN THE MANAGEMENT OF INFANTILE DIARRHEAS. ARTURO J. ABALLI, Rev. cubana pediat. **25**:1 (Jan.) 1953.

The author discusses the importance of laboratory methods in the management of diarrheal diseases. The importance of stool cultures, microscopic examination of the stools, and evaluation of the electrolyte status of the patient is emphasized. Nothing original is presented.

NELSON, San Francisco.

CHLORTETRACYCLINE (AUREOMYCIN), CHLORAMPHENICOL (CHLOROMYCETIN), AND OXYTETRACYCLINE (TERRAMYCIN) IN THE TREATMENT OF DIARRHEAS OF INFANCY. AGUSTIN CASTELLANOS, Rev. cubana pediat. **25**:20 (Jan.) 1953.

This is a summary of the properties, dosage, and effectiveness of these drugs in diarrheal diseases. Some of the literature on the subject is reviewed. No significant new observations are made.

NELSON, San Francisco.

TRUE PANCREATIC CYST IN INFANCY: REPORT OF A CASE. ALBERTO CALDERIN GOMEZ, Rev. cubana pediat. **25**:246 (April) 1953.

A case is presented of a single true pancreatic cyst in a child 2 years and 11 months of age treated by surgical excision. The article includes a general discussion of pancreatic cysts.

NELSON, San Francisco.

A Note on the Postmortem Findings of Children with Epidemic Jaundice. K. Gross and A. Traplova, Pediat. listy **6**:208, 1951.

A detailed description of the pathological anatomy of seven cases is given. The variations in the bioptic picture are stressed and explained. From the Authors' Summary.

Nervous Diseases

Effects of Intensive Psychotherapy on Epileptic Children: Report on Three Children with Idiopathic Epilepsy. Louis A. Gottschalk, A. M. A. Arch. Neurol. & Psychiat. **70**:361 (Sept.) 1953.

Three epileptic children were subjected to intensive psychotherapy. Seizures of two of the children have not returned after a period of two years, and those of the third child were notably decreased. The form of the ictal manifestations as well as the seizure frequency was modified during therapy.

The author feels that these cases furnish evidence to support a thesis that interpersonal events as well as intrapersonal conflicts can activate epileptic behavior.

McGuigan, Evanston, Ill.

Guillain-Barré Syndrome Treated with Corticotropin (ACTH). Arthur Blood, William Locke, and Ralph Carabasi, J. A. M. A. **152**:139 (May 9) 1953.

A case of Guillain-Barré syndrome is reported in which improvement followed administration of corticotropin (ACTH), relapse occurred in discontinuance of its administration, and improvement again followed administration of a second course of the hormone.

Kimball, Evanston, Ill.

Studies in Disorders of Muscle: VII. Clinical Manifestations and Inheritance of a Type of Periodic Paralysis Without Hypopotassemia. F. H. Tyler, F. E. Stephens, F. D. Gunn, and G. T. Perkoff, J. Clin. Invest. **30**:492 (May) 1951.

The report by several investigators in 1937 and 1938 that the paralytic attacks in periodic paralysis were associated with depressed serum potassium values led to the conclusion that the disorder is the consequence of a fault in the regulation of serum potassium levels. Later, Talbot summarized the data concerning 400 cases of periodic paralysis. The disorder has usually been referred to as familial, or family, periodic paralysis. It seems best, as Talbot pointed out, to call the disease periodic paralysis, specifying the hereditary nature of the disorder when it is genetically determined and referring to the other cases as sporadic, specifying the mechanism involved being specified where it is known. Talbot concluded that the syndrome probably represented a clinical entity due to a single metabolic dysfunction.

In the present study of a kindred in which 33 cases of clinically typical periodic paralysis were known to have occurred, the authors observed no striking hypopotassemia during attacks in the patients whom they studied in detail. This led them to an analysis of the genetic pattern in this kindred and a reevaluation of the data in this disorder. They studied methods of precipitating attacks, the effect of administering glucose or glucose and insulin, the effect of exercise and of enforced rest, and the correlation of these factors with serum potassium, sodium, magnesium, and phosphate levels, and with the blood glucose level. Gross and microscopic examinations of biopsy material from skeletal muscle, as well as determination of its glycogen content also were carried out.

Tyler and his co-workers found that clinically the disorder begins in infancy with recurrent attacks of weakness of flaccid paralysis. Some extensor weakness and enlargement of muscles are evident at all times. The attacks are most consistently produced by vigorous exercise followed by complete rest. No correlation of the attacks with the serum potassium or other electrolyte concentrations could be established.

An unusual pathologic picture of vacuolation of scattered muscle fibers was found in biopsy material. Neither fat nor glycogen could be demonstrated in the vacuoles, and it is presumed that they contained only edema fluid.

The pattern of inheritance is that characteristic of a simple Mendelian dominant trait with complete penetrance.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ANGIOGRAPHY IN A CASE OF HYDRANENCEPHALY. H. E. THELANDER, EDWARD B. SHAW, and JOHN J. PIEL, J. Pediat. **42**:680 (June) 1953.

This study was made with the hope that angiography would give additional information regarding the etiology of hydranencephaly. In this patient the vascular pattern was intact. They conclude that congenital cystic formation within the cerebral tissue was the probable cause of the malformation in this person.

MACDONALD, Pittsburgh.

TRANSPLACENTAL TRANSMISSION OF WESTERN EQUINE ENCEPHALOMYELITIS. HENRY R. SHINEFIELD and THOMAS E. TOWNSEND, J. Pediat. **43**:21 (July) 1953.

The authors report two cases of western equine encephalomyelitis in twin infants 5 days old. The evidence suggests transplacental transmission of the virus. Since maternal infection with western equine encephalomyelitis in the late stages of pregnancy does not invariably infect the infant, the authors suggest that in utero infection may be dependent upon local placental defects.

MACDONALD, Pittsburgh.

WESTERN EQUINE ENCEPHALOMYELITIS. ROBERT COHEN, ROBERT E. O'CONNOR, THOMAS E. TOWNSEND, PATRICIA ANN WEBB, and ROBERT W. MCKEY, J. Pediat. **43**:26 (July) 1953.

The authors report a clinical study of 42 cases of western equine encephalomyelitis. All of these patients survived. Some patients had residual symptoms.

The authors review the symptoms encountered in various age groups in children. They note that drowsiness is not a universal characteristic of this disease.

MACDONALD, Pittsburgh.

OBSERVATIONS ON THE EFFECT OF INDUCED HYPERGLYCEMIA ON THE GLUCOSE CONTENT OF THE CEREBROSPINAL FLUID IN PATIENTS WITH HYDROCEPHALUS. JOSÉ E. SIFONTES, R. D. BROOKE WILLIAMS, EDITH M. LINCOLN, and HELEN CLEMONS, J. Pediat. **43**:243 (Sept.) 1953.

The authors artificially induced hyperglycemia in children with and without hydrocephalus. In patients free from hydrocephalus, there was a significant increase in the glucose content of the cerebrospinal fluid. In patients with hydrocephalus but without active meningitis or spinal block due to tuberculous meningitis, artificially induced hyperglycemia failed to produce a significant increase in the content of the ventricular, cisternal, and lumbar fluid. In the presence of spinal block due to tuberculous meningitis, artificially induced hyperglycemia produced a significant elevation of the lumbar glucose curve, even when hydrocephalus was present.

MACDONALD, Pittsburgh.

CHOREA MINOR. J. SCHWARTZMAN, J. B. ZAONTZ, and H. LUBOW, J. Pediat. **43**:278 (Sept.) 1953.

Schwartzman, Zaontz, and Lubow report that the results of the use of corticotropin (ACTH) and cortisone in the treatment of chorea have been equivocal. Proponents have claimed that the reason for failure is inadequate dosage. At the same time, it has been pointed out that these products might suppress the activity of the adrenal or the pituitary. With this in mind, the authors used a combination of corticotropin and cortisone. They reasoned that with this combination, using small doses of each agent, they could obtain a sum that would produce a clinical effect with less suppression of glandular activity.

They treated six children with chorea. All recovered. Maximum therapy was 32 days. Best results appeared to occur with combinations in which the corticotropin-cortisone ratios approached each other. Three of their patients developed genitourinary infections while under hormonal treatment. These infections were cleared with antibiotics.

MACDONALD, Pittsburgh.

HAMARTOMA OF THE HYPOTHALAMUS. P. M. MARCUSE, R. A. BURGER, and G. W. SALMON, J. Pediat. **43**:301 (Sept.) 1953.

The authors report two cases of hamartoma of the hypothalamus. In contrast to the five cases previously reported in the literature, neither of the cases here have any signs of precocious sexual development. Both patients here had additional developmental defects.

MACDONALD, Pittsburgh.

ELECTROENCEPHALOGRAPHIC STUDIES IN CEREBRAL ANGIOMA. D. P. ROSENBERG, J. Neurol. Neurosurg. & Psychiat. **15**:260 (Nov.) 1952.

Rosenberg analyzed the electroencephalograms in 55 cases of proved cerebral angioma. He found that the EEG gave a lateralizing or localizing indication in 67% of the cases, the usual findings being localized 6 to 7 cps activity and/or high-voltage 2 to 3 cps waves showing phase reversal over the site of the lesion. These changes, with minor variations, are usually seen with other forms of cerebral tumor.

In discussing the value of electroencephalography as a diagnostic aid in angioma, the author notes that no specific EEG disturbance diagnostic of angioma could be seen in the 94 records of the 55 patients. In general, an angioma gives a EEG picture similar to that of cerebral tumor, which characteristically shows localized high-voltage irregular delta waves. However, the impression is that, with angioma, increased intracranial pressure and the spread of edema play, on the whole, a less important part than in cases of tumor, giving less generalized delta activity that will obscure a true focus and allowing a clearer localization of the intermediate slow activity. The same distinction serves to differentiate angioma from cerebral abscess, where, in addition, the slow delta waves at ½ to 2 cps are usual. The determination of pathology by the EEG is at best uncertain.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE SPINAL FLUID IN THE INFLAMMATORY DISEASES OF THE MENINGES IN CHILDHOOD. HANS SCHONENBERG, Ann. pædiat. **181**:65 (Aug.) 1953.

The liquor-cell picture in the acute and chronic bacterial and abacterial diseases of the meninges in childhood is more protean than is usually assumed; the participation of endothelial and histiocyte-cell elements has to be especially emphasized. In accordance with the morphological changes in the meninges in different illnesses the liquor-cell picture permits certain conclusions of a general nature with regard to the character and probable duration of the inflammatory process. The strong phagocytosis of the liquor cells in meningococcal meningitides is striking. The participation of endothelial and histiocyte cell elements in virus and leptospira meningitis is remarkable. The proponderance of lymphocytes in the liquor in tuberculous meningitis could not be confirmed.

FROM THE AUTHOR'S SUMMARY.

PHYSICAL REHABILITATION OF A CASE OF HEMIPLEGIA. ERNESTO SALDIAS, Rev. chilena pediat. **24**:243 (July) 1953.

Saldias reports physical rehabilitation of a bedridden patient with traumatic hemiplegia. This patient recovered functionally at the end of four months of treatment. The success of this case was due to the exact description of activities. A correct diagnosis and physical findings were very important in the treatment.

FROM THE AUTHOR'S SUMMARY.

LATE DEAFNESS FOLLOWING DIHYDROSTREPTOMYCIN. VELASCO, PAUL L., Rev. otorrinolaring. **22**:102 (Dec.) 1952.

In comparing the toxic effects of streptomycin and dihydrostreptomycin on the eighth nerve, Velasco has noted some rather interesting findings. In a series of 58 patients, 30 treated with streptomycin and 28 with dihydrostreptomycin, he found that the vestibular portion of the eighth nerve was involved in 13 and 11, respectively, even though the daily dosage of each drug was only 1 gm. The cochlear portion did not show any immediate involvement. However, Velasco observed an additional series of six patients in which dihydrostreptomycin was used, and noted no immediate cochlear or vestibular disturbances, but in each patient after one to two months tinnitus, usually bilateral, developed and a progressive deafness definitely of the perceptive type. The vestibular function was not disturbed in these patients. The deafness was of a permanent nature and did not improve under any type of medication. Velasco concludes that dihydrostreptomycin more frequently than streptomycin produces late toxic effects on the eighth nerve and, in consequences, advises that streptomycin be the drug of choice.

PERSKY, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

Psychology and Psychiatry

SPEECH EXAMINATION OF A GROUP OF INSTITUTIONALIZED MENTALLY HANDICAPPED CHILDREN. BERNARD B. SCHLANGER, J. Speech & Hearing Disorders **18**:339-349 (Dec.) 1953.

Seventy-four mentally retarded children, enrolled in St. Coletta's School for Exceptional Children, when studied for articulatory proficiency showed 30% hearing losses and marked deficiency in auditory memory span for vowels and sound discrimination. Syllable and tapping rates were slow and in general their speech was immature. Scores on formal testing with picture stimuli differed from conversation scores. Interrelationships between the five measures presumed to affect articulatory proficiency indicated that these measures were not related to a highly significant degree, with the exception of the maximum repetitive rates for syllable production and tapping.

PALMER, Wichita, Kan.

THE GENESIS OF ANTISOCIAL ACTING OUT IN CHILDREN AND ADULTS. ADELAIDE M. JOHNSON and S. A. SZUREK, Psychoanalyt. Quart. **21**:323 (July) 1952.

Johnson and Szurek synthesize the concepts on antisocial acting out which they have developed over the past decade. They state that their observations apply equally to the young "delinquent" and to the "psychopathic personality" of later years, who is etiologically a delinquent grown older. By means of collaborative therapy of children and parents, the authors have observed that the parents may unwittingly seduce the child into acting out the parents' own poorly integrated forbidden impulses, thereby achieving vicarious gratification. A specific supergo defect in the child is seen as a duplication of a similar distortion in the organization of a parent's own personality. The outcome is doubly destructive toward the child's and the parent's ego organization unless adequate therapy of both is provided.

WERMUTH, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

MANAGEMENT OF HEALTHY CHILDREN WHO "WON'T SLEEP." MORRIS WITKIN, South African M. J. **27**:902 (Oct. 10) 1953.

Sleep requirements are largely a matter of habit, and proper routine should be established early. Sleep refusal is mainly due to oversolicitous parents or nurses. Also, common causes are fear of the dark, physiological discomforts, unsuitable clothing and bedding, noises, faulty environments, or wrong feeding.

The family must have an understanding of child psychology and should radiate confidence in the child's sleeping habits.

MCGUIGAN, Evanston, Ill.

About the Significance of Lenticular Changes in Mongolism. Joseph Igersheimer and Hans Mautner, Ann. pædiat. **181**:34 (July) 1953.

Slitlamp studies were performed on 165 Mongoloids; 8% of the Mongoloids show coarse, large, and probably congenital cataracts which often lead to blindness and are probably the sequel of a damage in the first months of pregnancy. The cataracts are not characteristic for Mongolism.

Apart from these cataracts, practically every Mongoloid patient older than 17 years of age shows in the slitlamp picture characteristic findings of very many small cataracts, point-sized or flake-like, often hundreds of such opacities, which are greyish, often also bluish or greenish colored and which are not seen in the nucleus and are very rarely subcapsular.

This characteristic picture is not seen in children in the first six years of life. They develop slowly at the ages of 6 to 17 years. We were able to follow the development of the lenticular changes in a series of children. These findings are probably not connected with a damage in early gestation.

Similar findings were described and also seen by us in two other diseases, in myotonia dystrophica and in senile cataracts, which both are gene-determined conditions. The late development of lenticular changes in nearly every Mongoloid patient does not correspond to many current theories. A gene-determined tendency to cataracts (Buschke) would not explain the development of Mongolism either.

It seems the most probable theory that the development of these small lenticular opacities are signs of an early aging and degeneration in Mongoloids, similar to the occurrence in the gene-determined diseases, the myotomia dystrophica and the senile cataracts.

From the Authors' Summary.

Diagnostic and Prognostic Difficulties in Child Psychiatry (Neurotic Behavior to Schizophrenia). M. Schachter, Acta pediat. Espan. **11**:143-150 (Feb.) 1953.

The author presents the case of a youth observed from the 11th to the 18th year. The early symptoms were not unusual, such as nail biting, masturbation, stealing from his parents, and tyrannical behavior.

Details of his Rorschach responses and the family history are given. The father was over-strict; the mother infantilized the boy. He was an only child.

The author feels that he underestimated the seriousness of this boy's symptoms, as diagnosis is often difficult; there is an understandable hesitancy in labelling a prepuberal child schizophrenic or psychopathic. However, this patient developed a full-blown schizophrenia at the age of 16 years. He improved on insulin shock, but the prognosis is guarded.

The details of behavior from the so-called banal childish habits to more serious disturbances are described.

Allen, Santa Fe, N. Mex.

The Reaction of Children to Hospital Environment. L. Srp, Pediat. listy **8**:292, 1953.

The effect of hospital environment on 368 children was studied in a number of situations. Calm reactions to emotional stimuli become less numerous with decreasing age, there being a marked jump between the ages of 5 and 6 years. Painful medical procedures constitute the most intense stimuli to excitement, 45% of all children reacted to them with clear signs of excitation, such as shouting, crying, and passive or active resistance. Emotional disturbance is also marked at times of parting with parents. A generally calm reaction is shown by only 43% of the children under 5 years of age. It is recommended that more attention be paid to psychoprophylaxis and psychotherapy.

From the Author's Summary.

Psychogenic Obesity in Children. I. Torben Iversen, Acta pædiat. **42**:8 (Jan.) 1953.

Forty obese children, 15 boys and 25 girls 4 to 14 years of age, were examined with a view to psychogenic factors.

The children had been admitted to the Pediatrics Department, University Clinic at Rigshospitalet, Copenhagen, and to the Dronning Louise's Children's Hospital, Copenhagen.

Psychogenic factors were ascertained in 16 children, nine boys and seven girls. In 13 of these children, eight boys and five girls, the obesity had developed after the first three years of life.

In the remaining 24 children, six boys and 18 girls, psychogenic factors were questionable or nonexisting. In 13 of these children, one boy and 12 girls, the obesity had begun during the first three years of life.

A nonrejecting maternal overprotection was disclosed in 20 cases.

Varying degrees of emotional disturbances of difficulties of adjustment were recorded in 26 cases.

FROM THE AUTHOR'S SUMMARY.

ON PSYCHOGENIC OBESITY IN CHILDREN. III. FLEMMING QUAADE, Acta pædiat. **42**:191 (May) 1953.

The principal argument can be laid down as follows:

1. Obesity in childhood must have an alimentary cause.

2. Obesity in children seems to be a not very specific manifestation, provoked by such numerous incompatible and complicated psychological components as decide the attitude of the children and their surroundings concerning the taking and giving of food. Most important are the qualitative and quantitative dietary habits of the surroundings, and they are presumably founded on geography, ethnology, popular hygienics, and religion.

3. Etiology should, therefore be sought in each separate case and therapeutic endeavors adapted accordingly, the latter probably aiming at nutriohygienic instruction of the child and its surroundings plus psychotherapeutic treatment in such cases where mental difficulties caused by obesity should require it.

4. Prophylactic measures against adiposity in childhood should presumably consist of intensi fied nutriohygienic education of the population generally.

FROM THE AUTHOR'S SUMMARY.

Diseases of Genitourinary Tract

EFFECT OF STIMULATION OF THE REPRODUCTIVE ORGANS OF THE COW ON THE RELEASE OF AN OXYTOCIN-LIKE SUBSTANCE. R. L. HAYS and N. L. VANDEMARK, Endocrinology **52**:634-637 (June) 1953.

The purpose of this study was to determine the effect of stimulation of the reproductive organs of the cow by artificial insemination techniques and natural mating on the release of oxytocin as measured by increased intramammary pressure.

The positive response of increased intramammary pressure indicates that stimulation of the reproductive organs of the cow causes milk ejection. The nerve impulses initiated by the stimulation conceivably cause the release of a hormone which brings about the ejection. Since it has been shown that cutting the nerve supply of the mammary gland does not interfere with normal milk ejection and that stimulation of the known nerves to the udder does not cause milk ejection, the possibility of reflex action is remote. The facts that the responses occurred in 10 to 30 seconds after stimulation and that the effective substance is released into the blood after stimulation indicate that it is a hormone.

It is postulated that stimulation of the reproductive organs of the cow causes the release of oxytocin.

JACOBSEN, Buffalo.

NEUROGENIC EFFECTS OF UTERINE DISTENTION ON THE ESTROUS CYCLE OF THE EWE. WARD W. MOORE and ANDREW V. NALBANDOV, Endocrinology **53**:1-10 (July) 1953.

The role of the uterus and its innervation in the regulation of cyclic reproductive phenomena and in the maintenance of corpora lutea has been little studied.

It is well established that a neurohumoral link exists between the uterine cervix and the anterior pituitary gland. Such a connection between the uterine cornua or uterine body and the pituitary gland has been suspected but has never been shown to exist.

This study indicates that the uterus, through its afferent endings, has a regulatory effect on the events which make up the estrous cycle of the ewe. Although this phenomenon has been shown in only one species, similar regulation by the uterus on the pituitary-ovary axis may

exist in other spontaneously ovulating species. The following facts were demonstrated by the experiments described:

1. Distention of the uterine cornu of the cycling ewe under the hormonal conditions present during the early luteal phase of the reproductive cycle alters the endocrine activity of the pituitary-ovary axis and causes a significant shortening of the estrous cycle from 16.3 to 11.9 days.

2. The maintenance of normal cycles (16.1 days) in ewes following distention of a denervated segment of the uterus indicates that this phenomenon is mediated over nervous pathways. Denervation alone does not affect the length of the estrous cycle (16.2 days).

3. Evidence is presented which indicates that following uterine distention there may be an increase in the secretion of follicle-stimulating hormone, luteinizing hormone, and luteotrophin. Possible mechanisms of these changes are discussed. JACOBSEN, Buffalo.

CAN THE OVARIAN HORMONES INHIBIT THE MAMMARY RESPONSE TO PROLACTIN? JOSEPH MEITES and JAMES T. SGOURIS, Endocrinology **53**:17-23 (July) 1953.

The question as to why lactation is not normally initiated during pregnancy still remains unanswered. The concept which has probably gained widest acceptance is that the ovarian hormones, particularly estrogens, inhibit the secretion of prolactin by the pituitary. This view is held despite the fact that no direct evidence has yet demonstrated that the ovarian hormones can reduce prolactin either in the pituitary or circulation. From the experiments here reported it is concluded that in the doses employed, estrone and progesterone together can effectively inhibit the milk-secreting action of prolactin on the mammary gland of the rabbit, whereas progesterone alone is ineffective and esterone alone is only slightly effective in this respect.

JACOBSEN, Buffalo.

SOURCES OF RELAXIN IN THE RABBIT. M. X. ZARROW and R. ROSENBERG, Endocrinology **53**:593-598 (Dec.) 1953.

In view of the many possible sources of relaxin noted among different species, this study was undertaken to determine the major source of the hormone in a single species, the rabbit. In view of the failure of castration to affect the normal pregnancy levels of relaxin in the blood and the relatively high concentration in maternal placenta, it was concluded that the placenta is probably the most significant source of relaxin during pregnancy.

It would appear that in the rabbit, under suitable conditions, the ovaries, uterus, placenta, and vagina may all secrete relaxin. JACOBSEN, Buffalo.

EFFECTS OF THE MENSTRUAL CYCLE ON THE METABOLISM OF HUMAN ENDOMETRIUM. DWAIN D. HAGERMAN and CLAUDE A. VILLEE, Endocrinology **53**:667-673 (Dec.) 1953.

The data presented in this paper show that cyclic variation in the metabolism of human endometrium exists, and that the metabolic effects of estrogen in vivo and in vitro are identical.

JACOBSEN, Buffalo.

STUDIES AS TO THE KIDNEY FUNCTION OF INFANTS. L. PARENZAN and F. SERENI, Pediatria **61**:665 (Sept.) 1953.

Three renal function tests were made on each of a group of 61 infants whose ages ranged from 40 days to 20 months. Glomerular filtration values were found to be low until the child reached the age of 9 months. Renal plasma flow was also below the adult level for the first 18 months of life. The rate of excretion of *p*-aminohippuric acid in all the infants studied, was definitely below that found in adults. HIGGINS, Boston.

LIPOID NEPHRITIS: ITS AUTONOMY, CLINICAL AND NOSOLOGICAL TREATMENT. JUAN P. GABRAHAN, Rev. españ. pediat. **9**:703 (July-Aug.) 1953.

Basing his comments on the study of 50 children with lipoid nephrosis, the author insists it is a clinical and nosological entity and points out the diagnostic differences. Although one-third of his cases have apparently proceeded to complete cure, he states there is no specific therapy other than the correction of nutritional defects and intercurrent infections. His experience with corticotropin (ACTH) and cortisone leads him to feel that these are ineffective in the treatment of lipoid nephrosis. ALLEN, Santa Fe, N. Mex.

FALSE ENURESIS. R. HEFFINCK, Acta pædiat. belg. **5**:127, 1951.

A girl aged 5 years was brought for examination because of enuresis, day and night. On inspection one could see continual wetting in the form of small amounts of urine ejected periodically. Inspection of this urine and comparison with urine obtained by catheterization from the bladder showed difference in color. It became obvious that two urinary openings existed, and injection of contrast medium into the lateral opening showed in the roentgenogram a large dilated ureter which ended in separate calyces on the left.

On operation two normal kidneys were found plus a third kidney attached to the left normal kidney and emptying separately into the dilated ureter. This third kidney was removed surgically.

GLASER, Jerusalem.

CYSTORADIOGRAPHY IN INFANTS AND OLDER CHILDREN. A. RUBIN and O. SNOBL, Pediat. listy **8**:246, 1953.

A modified method of cystoradiographic examination with special reference to technique and difficulties of procedure is described. The work is based on 41 examinations.

FROM THE AUTHORS' SUMMARY.

A CREATININE TOLERANCE TEST FOR RENAL FUNCTION. ALFRED SUNDAL, Acta pædiat. **42**:535 (Nov.) 1953.

The creatinine curve in blood plasma after an oral creatinine load is a test which gives important information about kidney function. Without needing urine collection—a procedure often difficult in infants and also in some cases with urinary disease even when collected by catheter—the blood creatinine fall gives values corresponding to the exogenous creatinine clearance test, and also to the endogenous creatinine clearance test, provided the patient is not in a preedematous or edematous stage. The author gives the values for creatinine fall in the blood in healthy children and in patients with decreased kidney function after an empirically chosen creatinine load.

FROM THE AUTHOR'S SUMMARY.

THE PROGNOSIS OF GLOMERULONEPHRITIS IN CHILDREN. E. CHELI and F. AMORE, Clin. pediat. **35**:555 (Aug.) 1953.

Two hundred seventeen children with acute glomerulonephritis were treated at the pediatric clinic of the University of Modena in the course of the past 18 years. In 5 of the 18 years, 20 or more cases were treated, while in 6 of the years, 6 or fewer cases were treated. Fifty-six per cent of the cases were in boys; 61% of the cases began in the months September to February. In only 63% of the cases could a definite history of a preceding streptococcic infection be obtained. Sixteen of the children died in the acute phases of glomerulonephritis; five died from an unrelated cause. Six of the deaths were in children under one year of age. On a follow-up study of 102 cases, 16 showed slight pathological urinary findings, while only one showed the changes of a chronic glomerulonephritis.

HIGGINS, Boston.

Diseases of Ductless Glands; Endocrinology

EFFECTS OF HYPOTHALAMIC LESIONS AND SUBSEQUENT PROPYLTHIOURACIL TREATMENT ON PITUITARY STRUCTURE AND FUNCTION IN THE RAT. E. M. BOGDANOVE and N. S. HALMI, Endocrinology **53**:274 (Sept.) 1953.

There is increasing evidence that many phases of anterior pituitary activity can be impaired by damaging either the hypothalamus or its neural or vascular connections with the hypophysis. These investigations were designed to relate functional alterations of the adenohypophysis produced in this way to concomitant morphological changes of the gland, the latter being examined by recently devised staining techniques which have considerably clarified the histophysiology of the pituitary in the rat.

Bilateral electrolytic lesions were placed in various hypothalamic regions of adult male rats which were subsequently treated with propylthiouracil for periods ranging from 10 to 21 days.

In a number of these animals one or more of the following sequelae of the lesions, varying in severity, were observed to occur: (*a*) impairment of the hyperplastic response of the thyroid to propylthiouracil, but no concomitant interference with the goitrogen-induced elevation of the thyroid: serum iodide concentration ratio, (*b*) gonad atrophy of the hypophysectomy type with commensurate regression of the accessory sex glands, (*c*) cryptorchid-like testicular alterations, (*d*) hyperplastic changes of the intermediate hypophysial lobe, (*e*) atrophy of the neurohypophysis, (*f*) obesity, (*g*) savage behavior.

JACOBSEN, Buffalo.

DEMONSTRATION OF STORAGE AND RELEASE OF GONADOTROPIN BY THE ANTERIOR PITUITARY OF THE MOUSE DURING GESTATION. AARON J. LADMAN and MEREDITH N. RUNNER, Endocrinology **53**:367 (Oct.) 1953.

Two current concepts of pituitary function are: (1) that the anterior pituitary is relatively inactive with respect to manufacture and release of gonadotropins during pregnancy, and (2) that variation in gonadotropic content may denote either a change in rate of production or an alteration in rate of discharge.

The experiments here reported, designed to test these hypotheses, indicate that the anterior pituitary of the mouse during pregnancy is a very active gland. In regard to the second question, the results indicate that measurement of the degree of pituitary activity depends upon quantitative variation in storage and release of pituitary gonadotropin.

JACOBSEN, Buffalo.

THE EFFECT OF PROGESTERONE ON PERSISTENT VAGINAL ESTRUS PRODUCED BY HYPOTHALAMIC LESIONS IN THE RAT. MONTE A. GREER, Endocrinology **53**:380 (Oct.) 1953.

There is much evidence indicating that the central nervous system is of importance in the regulation of the hypophysial secretion of gonadotrophic hormones. Present evidence favors the hypothesis that such control is mediated by neurohumors passing through the hypophysial portal system, but the precise nature of such control has not as yet been clearly defined.

The present investigation was undertaken to extend the observations of the effect of hypothalamic lesions on reproductive activity in the rat. It was found that in those animals in which persistent estrus was produced, cyclic ovarian activity and endogenous progesterone production could be induced by the daily administration of small doses of progesterone.

JACOBSEN, Buffalo.

THE INFLUENCE OF THE ADRENAL CORTEX AND COLD STRESS ON FASTING KETOSIS IN THE RAT. JAMES L. SCOTT JR. and FRANK L. ENGEL, Endocrinology **53**:410 (Oct.) 1953.

Ketosis has been considered to be a part of the "alarm reaction" and as such conceivably mediated by or dependent upon adrenal cortex activity.

The present studies were designed to elucidate some of the factors involved in the ketosis of stress and its relation to the adrenal cortex. For this purpose, cold exposure was chosen as the stressor and the effects of corticotropin (ACTH), cortisone, and hydrocortisone tested. It was found that cold exposure, resulted in a marked increase in fasting ketosis, while cortisone and hydrocortisone treatment suppressed fasting ketosis, both at normal and low environmental temperatures.

JACOBSEN, Buffalo.

STEROID DIABETES IN GUINEA PIGS: EFFECTS OF CORTISONE ADMINISTRATION ON BLOOD, AND URINARY GLUCOSE, NITROGEN EXCRETION, FAT DEPOSITION, AND THE ISLETS OF LANGERHANS. FRANZ X. HAUSBERGER and ANDREW J. RAMSAY, Endocrinology **53**:423 (Oct.) 1953.

The 11-oxygenated corticosteroids and corticotropin (ACTH) have the well-known property of aggravating an existing diabetes in humans, rats, dogs, and cats. In normal rats, however, a steroid diabetes can be induced only by simultaneous force-feeding.

This study presents a report on cortisone diabetes in guinea pigs with free access to food. This diabetes resembles in many respects Cushing's syndrome in man but differs from the steroid diabetes in force-fed rats. The most striking observations in the cortisone-treated guinea pig were an extraordinary hypertrophy of the islets of the pancreas, increased gain of weight, obesity, and a positive or slightly positive nitrogen balance.

JACOBSEN, Buffalo.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

MYASTHENIA GRAVIS PSEUDOPARALYTICA IN CHILDHOOD AND ITS COMBINATION WITH EXOPHTHALMIC GOITER. HUGO ALTHOFF and INGEBORG FLOER, Deutsche med. Wchnschr. **78**:1262 (Sept. 11) 1953.

A girl 5½ years old was admitted to the hospital with an exophthalmic goiter which yielded to treatment with propylthiouracil. Three months after dismissal, a ptosis of the right upper eyelid was noted. Various tests secured the diagnosis of myasthenia gravis pseudoparalytica.

AMBERG, Rochester, Minn.

CHRONIC ARTHRITIS IN CHILDREN. J. HOUSTEK and D. SRBOVA, Pediat. listy **8**:261, 1953.

Seventeen cases of Still's syndrome and 19 cases of primary chronic arthritis are reviewed with a discussion of the clinical picture, frequency, and significance of the various signs. A case is described of a special form of chronic arthritis with a psoriasiform rash and affection of the valvular apparatus. Therapy and results with corticotropin (ACTH), cortisone, and gold sodium thiomalate (Myochrysine) are surveyed.

FROM THE AUTHORS' SUMMARY.

ON THE ETIOLOGY OF DYSOSTOSIS MANDIBULOFACIALIS. HELGE GRANRUD, Acta pædiat. **42**:499 (Nov.) 1953.

Five cases of dysostosis mandibulofacialis are recorded. In all of them there are exogenic factors which may possibly account for the deformities. Particular attention has been paid to one case where an abortion was attempted during the fifth week of pregnancy.

FROM THE AUTHOR'S SUMMARY.

Diseases of Eye

CLINICAL SIGNIFICANCE OF SOME CONGENITAL CHANGES IN THE OPTIC DISK. ARTHUR J. BEDELL, J. A. M. A. **151**:95 (Jan. 10) 1953.

Before discussing some of the congenital changes of the optic disk, the author reviews the wide physiological variations in size, color, and general configuration which may occur in the so-called normal disk. He calls especial attention to the relations of the central excavation to the early diagnosis of glaucoma, papilledema, and papillitis.

The congenital anomalies discussed include medullated nerve fibers, remnants of Cloquet's canal, vestiges of Bergmeister's papilla and unusually large residues, falciform folds of the retina, pseudo-choked-disks, inverted disk, "holes" or "pits" in the disk, some staphylomas, posterior vortex veins in or close to the margin of the scleral rim, and congenitally abnormal vessels. Several illustrative plates are shown.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

RETRACTION NYSTAGMUS AS A FOCAL SIGN. V. TRONCONI, Riv. oto-neuro-oftal. **24**:195 (March-April) 1949.

Twelve cases of retraction nystagmus have appeared in the literature since it was first described by Körber, in 1903. A girl aged 14 complained of headaches and vomited frequently. She had attacks of mental dulness and brief periods of loss of consciousness. No abnormal movements were noted. In her admission to the hospital, there was paralysis of the right external rectus muscle in upward conjugate gaze. The Roth-Bielchowsky reflex was intact.

During convergence and with upward gaze retraction of the eyeball was noted. An extensor response was elicited on stimulation of the soles, and an Oppenheim sign was present bilaterally. The patient fell backward when standing up. Papilledema was present bilaterally. Retraction nystagmus was noted after the nystagmus induced by vestibular tests ceased. Optokinetic nystagmus with lateral movements was normal after the retraction nystagmus was noted. Optokinetic nystagmus was absent with upward gaze and was intact with downward gaze. Retraction nystagmus was present during optokinetic tests with upward and downward gaze. Ventriculography revealed marked dilatation of both lateral ventricles and the third ventricle. Iodoventriculography showed incomplete closure of the aqueduct. The ventricular fluid gave a mildly positive Pandy reaction, and contained two cells per cubic millimeter and 33 mg. of protein per 100 cc. The child died, but autopsy was not performed. Retraction nystagmus is considered to indicate a lesion in the mesencephalon in the region of the supranuclear oculomotor pathways. The resulting defect in innervation causes simultaneous contraction of agonists and antagonists, producing retraction of the eyeball rather than movement in a normal direction.

N. Savitsky, New York [A. M. A. Arch. Neurol. & Psychiat.].

Surgery and Orthopedics

The Use of Prosthesis for Limb Defects in Children. R. F. Chittenden, Am. J. Surg. **86**:128 (Aug.) 1953.

This is a summary of the author's observations on 34 amputee children. The need for individual attention to the problems of the amputee child, the difficulties encountered in the female from the standpoint of good cosmetic results, and the need for approach to the child at an earlier age than has been customary is stressed.

The author strongly advocates the use of plastic laminates in limb fabrication, as he feels that fitting by a casting technique offers many advantages to the young child. The article covers a considerable number of facets of the problem of limb prosthesis in all younger age groups.

From the Author's Summary.

Treatment of Developmental Malformations of the Jaws. J. M. Converse and H. H. Shapiro, Plast. & Reconstruct. Surg. **10**:316 (Nov.) 1952.

Converse and Shapiro present a classification of different jaw malformations resulting from faults in embryological development or disturbances of growth after birth. These abnormalities are analyzed, described in detail, and fully illustrated by outline and artist's drawings. Excellent photographs illustrate the before- and after-operation appearances. Four case histories serve to make a very clear presentation of the subject under consideration. A bibliography of 24 references is appended.

Seltzer, Philadelphia [A. M. A. Arch. Otolaryng.].

Treatment of Burns in Children. René Artigas Nambrard, Rev. chilena pediat. **24**:235 (July) 1953.

The general results obtained in the last 10 years in the treatment of burns are analyzed. Seventy-one case histories of patients hospitalized during the year 1951 are reviewed. Eight cases treated with cortisone are detailed.

From the Author's Summary.

Miscellaneous

Post Hoc, Ergo Propter Hoc. Stewart H. Clifford, J. Pediat. **43**:237 (Sept.) 1953.

Clifford says that progress in medicine has been so rapid that we have become conditioned to miracles, perhaps to an extent where our common sense and critical judgment have been deadened. Yet at no time has there been more need for sound medical judgment. Some of the vogues in medical treatment that need to be evaluated are vitamin K in the treatment of hemorrhagic disease of the newborn, oxygen in the treatment of the premature infant and its relation to retrolental fibroplasia, oxygen mist in the treatment of the hyaline-membrane syndrome, and the "Bloxsom air-lock" for resuscitation of the newborn infant. All of these need further critical evaluation.

Macdonald, Pittsburgh.

ENCEPHALOPATHY OCCURRING DURING THE TOPICAL USE OF ASTEROL. NORMAN GOLDSTEIN, **42**:726 (June) 1953.

Asterol (2-dimethylamino-6-[β-diethylaminoethoxy]-benzothiazole) dihydrochloride is a treatment for mycotic infections in humans. Topical therapy with Asterol may produce the following symptoms: convulsions, visual hallucinations and delirium, muscular weakness, and ataxia. Removal of the drug relieves the symptoms.

MACDONALD, Pittsburgh.

FIVE YEAR SURVEY OF MULTIPLE PREGNANCIES. R. C. ROSS and N. W. PHILPOTT, Canad. M. A. J. **69**:247 (Sept.) 1953.

Study of multiple pregnancies over a five-year period indicated that twin pregnancies were not a significant cause of prolonged labor. The fetal mortality rate of approximately 10% may best be reduced by preventing premature onset of labor. Some authors have suggested that all multiple pregnancy patients should be hospitalized for bed-rest at the beginning of the ninth month. In the series of multiple pregnancies, toxemia was seven times more frequent, placenta previa twice normal expectancy, postpartum hemorrhage four times more common, and manual removal of the placenta twice as frequent as in single pregnancies.

McGUIGAN, Evanston, Ill.

THE NUMBER OF CASES OF NEOPLASMS SEEN IN THE PEDIATRIC CLINIC OF PARMA FROM 1942 TO 1952. S. LO BIANCO, Lattante **24**:10 (Jan.) 1953.

Seventy of the 11,400 children admitted to the Pediatric Clinic of Parma in a 10-year period had tumors. Leukemia is not counted as a tumor. Thirty-four were angiomata (mostly in children under 2 years of age), 13 were tumors of the central nervous system, 7 were tumors of the kidneys, and 7, of the abdomen.

HIGGINS, Boston.

BACON FAT AS A THERAPEUTIC AGENT FOR THE PEDIATRICIAN. SEPP FOLBERTH, Deutsche Med. Wchnschr. **78**:45 (Nov. 6) 1953.

Fresh bacon fat contains the unsaturated fatty acids linolic, linolenic, and arachidonic acid, as does sunflower oil. The bacon fat is pickled for 12 hours and smoked without heating to light golden yellow and then scraped. It is added to the bottles or to vegetables. The fatty acids are not stable and cooking is not permissible. The youngest infant of 6-weeks-of-age tolerated it well. The fat is given in an amount of 5 gm. to start. The amount can be raised cautiously to 30 to 50 gm. Good results were obtained in cases of seborrheic dermatitis, eczema infantum, and milk crust. No cases are reported in greater detail.

AMBERG, Rochester, Minn.

News and Comment

GENERAL NEWS

Specialists Certified by The American Board of Pediatrics, Inc.—The following physicians were certified as specialists by The American Board of Pediatrics, Inc., in Indianapolis, on Dec. 4, 5, and 6, 1953.

Bansmer, Charlotte, Seattle.
Baskin, John Lane, Cameron, Texas.
Baxter, Paul, Seattle.
Bergener, Karl L., Kankakee, Ill.
Burdett, Ray E., Ogden, Utah.
Call, Justin David, Pleasanton, Calif.
Cohen, Merton E., Easton, Pa.
Craig, Joseph Deafner, Rochester, Minn.
Crouch, William Harvey, Jr., Topeka, Kans.
Dobrow, Bernard, San Jose, Calif.
Dugger, James A., Topeko, Kans.
Dzurik, Frank J., Cleveland.
Eberlein, Walter Rather, Boston.
Ehrenreich, Robert J., Camp Atterbury, Ind.
Etra, Bernard, Teaneck, N. J.
Fanney, Grafton Clinton, Jr., Euclid, Ohio.
Farrell, William J., Evergreen Park, Ill.
Galligan, John J., St. Paul.
Gibstine, Marvin H., St. Louis.
Goldenberg, Charles, Chicago.
Gustafson, Robert E., Sr., Kankakee, Ill.
Hebert, Hyland J., Manila, Phillippines.
Herbert, Wayne Iren, Whittier, Calif.
Hidey, Robert Marshall, Jr., San Francisco, Calif.
Holland, Hubert Rex, Paducah, Ky.
Jerome, Elizabeth K. B., Minneapolis.
Kamin, Peter Ben, Galveston, Texas.
Kelly, Richard Sterling, Jr., Fayetteville, N. C.
Kennell, John Hawks, Cleveland.
Kores, Vernon, Milwaukee.
Krempin, Herman Otis, Dallas, Texas.
Kuder, Howard V., Muncie, Ind.
Ledbetter, Marion Kenneth, Tulsa, Okla.
Leeds, John Franklin, Hot Springs, S. Dak.
Lundeberg, Palmer O., Chicago.
Markovitz, Jack, Chicago.
Maxwell, John Robert, Camp Stoneman, Calif.
Mickle, Kenneth Cochran, Green Bay, Wis.
Miller, Loren V., Yonkers, N. Y.
Mitchell, Henry, Indiana, Pa.
Olive, John Thomas, Jr., Junction City, Kans.
Palmer, Leo E., Dayton, Ohio.
Petersen, Deane Alfred, Minneapolis.
Phillips, Carey William, Jr., Portsmouth, Va.
Procopio, Frank, Harrisburg, Pa.
Pugh, David Franklin, Abilene, Texas.
Schneider, Albert John, Indianapolis.
Schwartz, Mervyn U., Tacoma, Wash.
Sepkowitz, Samuel, Oklahoma City.
Shadle, George M., Pittsburgh.
Shepard, Thomas Hill, II, Fairchild, Wash.
Sherman, Bennett Richard, Winnetka, Ill.
Stiles, Frank C., Monroe, Wis.
Suddarth, Sterling B., San Leandro, Calif.
Thiers, George Frederich, Pittsburgh.
Thompson, William West, Fort Sam Houston, Texas.
Thomson, John William, Grand Rapids, Mich.
Tomlinson, William Arthur, Springfield, Ill.
Winters, Kenneth J., Wauwatosa, Wis.

Tenth M & R Conference.—The 10th M & R Conference, sponsored by the M & R Laboratories, of Columbus, Ohio, was held on Nov. 19, under the auspices of the Department of Pediatrics of the State University of Iowa College of Medicine. The subject of the conference was "The Role of Vitamin B_6 in Human Nutrition." A group of outstanding authorities on the fundamental scientific aspects of the role of vitamin B_6 in metabolism and its application to clinical problems was assembled for this conference. Particular attention was given to the problem of the occurrence of convulsions in infants, which have been attributed to a deficiency of vitamin B_6. A summary of the papers presented and the discussions will soon be published by the M & R Laboratories for distribution to the profession. The conference was conducted under the chairmanship of Dr. Charles D. May, Professor and Chairman of the Department of Pediatrics of the State University of Iowa College of Medicine.

Scientific Meeting of Nassau Pediatric Society.—A scientific meeting of the Nassau Pediatric Society was held at the Garden City Hotel on Dec. 14, 1953. Dr. Harold Harrison, Associate Professor, The Johns Hopkins University School of Medicine, Chief Pediatrics, Baltimore City Hospital, spoke on the uses of cortisone and pituitary-stimulating hormones in diseases of children. He pointed out that there has been encouraging results in the use of these in rheumatic fever, nephrosis, serum sickness, purpura, and in some cases of arthritis. Although they have not cured leukemia, they have made the patients much more comfortable.

ANNOUNCEMENTS

Postgraduate Courses in Pediatrics.—Two postgraduate courses in pediatrics are being offered by the Department of Pediatrics, Harvard Medical School, at Massachusetts General Hospital, in June, 1954. The first, which will be from June 14 through 22, will deal with general pediatric problems. The second, on June 23 through June 25, will deal with endocrine and metabolic disorders in children and adolescents. Enrollment may be for either course or the total combined course. Those interested should write to Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston.

American College of Allergists.—The American College of Allergists will meet at the Roney-Plaza Hotel, Miami Beach, Fla., early in April. On Monday evening, April 5, from 8 to 10 p.m., there will be an evening panel discussion on allergy in "The Infant under Two," with Bret Ratner, M.D., as chairman. The Section on Pediatric Allergy will meet on Friday morning, Aril 9, with Jerome Glaser, M.D., as chairman. Friday afternoon there will be a round-table discussion on pediatric allergy with C. Collins-Williams, M.D., of Toronto, Canada, as moderator. Reservations should be made and luncheon tickets purchased at the registration desk on April 8, or this may be done earlier by writing Dr. Fred W. Wittich, Secretary, American College of Allergists, 401 La Salle Medical Bldg., Minneapolis 2.

Coming Examinations to Be Held by The American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations on Feb. 19, 20, and 21, 1954, in Washington, D. C., and on March 19, 20, and 21, 1954, in Des Moines, Iowa.

Information Requested on Dysproteinemia in Infancy.—Prof. A. Laurinsich, who will report on "Dysproteinemia in Infancy" at the next National Pediatrics Congress, is collecting as complete information on this subject as possible. If anyone working in this field has copies of publications or even references which they can send him, please address them as follows: A. Laurinsich, Clinica Pediatrica Universita, Parma, Italy.

Fellowships in Field of Cancer in Children.—Fellowships for training in clinical investigation in the field of cancer in children, including chemotherapy, have been created at the Children's Cancer Research Foundation. Stipends vary from $2,400 to $5,000, depending upon training. Application blanks may be secured from the office of Dr. Sidney Farber, Scientific Director, Children's Cancer Research Foundation, Boston.

Institutes in the Care of Premature Infants.—The Institutes for Physicians and Nurses in the Care of Premature Infants at the New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, are currently in their fifth year of operation. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses of four weeks' duration. Participants pay no tuition fee, and stipends are provided to help cover expenses during attendance at the Institute. The last Institute for the current fiscal year starts on May 17, 1954. Five Institutes will be held between Sept., 1954, and May, 1955. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, New York Hospital, 525 E. 68 St., New York 21.

Third International Poliomyelitis Conference.—The Third International Poliomyelitis Conference will be held in Rome, Italy, Sept. 6-10, 1954. Correspondence and inquiry regarding the Congress should be addressed to the secretariat of the Third International Poliomyelitis Conference, Via Lucullo 6, Rome, Italy. Telegraphic address: Inpolio, Rome.

Memorial Center for Cancer and Allied Diseases Announces Three-Day Course.—The Pediatric Service of the Memorial Center for Cancer and Allied Diseases announces a comprehensive three-day course, April 28, 29, and 30, 1954, for pediatricians, general practitioners, and health officers. Current developments and established methods in diagnosis, differential diagnosis, and management of benign and malignant tumors, Hodgkin's disease, leukemia, and reticuloendothelioses in childhood are included. The content of the course will be as follows: demonstrations, and examinations of children in pediatric, surgical, chemotherapy, and radiotherapy clinics; ward rounds and seminars, under the direction of the staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research. The fee is $35. For information, address the Director, Pediatric Service, Memorial Center, 444 E. 68th St., New York.

Books

Problems of Infancy and Childhood: Transactions of the Sixth Conference, March 17 and 18, 1952, New York, N. Y. Edited by Milton J. E. Senn, M.D. Price, $2.50. Pp. 160. Sponsored by Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1953.

Dr. Frank Fremont-Smith opened the conference with an outline of the purpose, the organization, and the method of conducting the Josiah Macy Jr. Foundation conference program.

The first discussion, led by Dr. Sibylle Escalona, deals with the "Emotional Development in the First Year of Life." These psychoanalytic observations on infant behavior can best be described in the author's own words as a "peculiar conglomeration of impressions, thoughts and fantasies." Descriptions of nursing, crying and sleeping, reactions of infants to mother and strangers, reaction to injections, etc. are given in detail with theoretical interpretations. Discussion takes place as to whether certain mother-child relationships should be described as resonance, contagion, or communication. Onset of anxiety is thought to begin between the fourth and eighth month. Two case histories are presented for comparison to demonstrate individual variations in emotional growth and development.

The second presentation is entitled "A Brief Review of W. H. O. Activities," by Knut Kjellberg. The World Health Organization provides consultations in various fields requested by the government represented. Mental health, rehabilitation of handicapped children, and vocational guidance are all activities directed by the World Health Organization.

The third discussion, entitled "Observations of Individual Tendencies in the First Year of Life," by Katherine M. Wolf, is a report of observation on mothers and babies from the sixth month of pregnancy to the first year of life. Attempts were made to evaluate clinically and to predict the future personality pattern of a small group of infants. From a case history presented, mother-child relationships are discussed relative to anxiety, fears, and resentment.

The final discussion on "Excessive Crying in Infants, a Family Disease," by Ann Stewart, emphasizes the importance of family environment, especially the feelings of mothers as a cause of crying. The cause of excessive crying is considered in relation to type, quantity, and frequency of feeding, the inherent sensitivity of the baby to food that the nursing mother has eaten, and to allergic states.

This book should be of interest to the psychoanalyst. From a pediatric standpoint it is difficult to accept any study of growth and development based on impressions, fantasies, and theories. Pediatrics has been very appreciative of the contributions made by psychiatry to our knowledge of emotional growth. However, we are accustomed to think of and observe emotional development in relationship to physical and mental growth; in the home as well as in the laboratory, and in relation to the whole family. Such accepted methods are in contrast to the present study. The volume has little of value to recommend it to the pediatrician.

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MEYENBERG EVAPORATED GOAT MILK has been prescribed by physicians since 1934 as a superior natural milk for patients allergic to Cow's Milk Lactalbumin. By specifying Meyenberg, you make certain of prescription-quality **Grade A goat milk,** sterilized after sealing in special vacuum packed enamel-lined cans. Available in 14 oz. cans at all pharmacies.

HI-PRO: SPECIALLY PREPARED SPRAY DRIED MODIFIED COW'S MILK to provide maximum protein levels without excessive fats or carbohydrates. A flexible basic milk food of exceptional value in the feeding of the infant with fat intolerance, for the premature or for routine feeding. **CONTAINS PROTEIN 41% – FAT 14%.** Available in 1 lb. vacuum tins at all pharmacies.

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pediatric
antihistamine

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A palatable, spice-flavored antihistamine, Pyribenzamine Elixir offers highly effective therapy in a broad range of allergies. *Dosage can be readily adjusted* to any age, any individual requirement. *Prescribe this well-accepted medication* alone or as a therapeutic vehicle. Each 4 cc. (approximately one teaspoonful) contains 30 mg. Pyribenzamine (tripelennamine) citrate (equivalent to 20 mg. Pyribenzamine hydrochloride). In pints and gallons.
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Ciba

Meat...

and Adequate Protein Nutrition of the Diabetic Patient

Although formerly it was considered desirable in diabetes mellitus to hold protein intake only slightly above minimal requirements in order to minimize metabolic activity, present day treatment recognizes distinct benefits resulting from liberal protein alimentation.[1] Generous allowances of protein heighten the patient's sense of well-being, improve vigor, and augment the organism's inherent protective forces.

For the adult diabetic, desirable daily allowances of protein range from 1 to 1.5 grams per kilogram of body weight.[1] To assure adequate amounts of protein for growth and maintenance in diabetic children, allowances should range from 2 to 3 grams per kilogram. Following acute episodes during periods of inadequate insulin treatment, the concomitant negative nitrogen balance calls for high protein feeding until lost nitrogen is restored.[2] Though caloric intake is restricted for correction of overweight, protein allowances remain unchanged.

Meat ranks high among the foods qualified to provide the desired amounts of protein in diabetic diets. In fact, meat—because its rich store of protein is of highest biologic value—may well contribute a large share of the diabetic's daily protein requirement.[3]

In addition, meat also provides important amounts of essential B vitamins and minerals. Its appetite appeal goes far in enabling the diabetic patient to stay on his prescribed diet.

---

1. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, pp. 287-299.

2. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition. Prepared with Collaboration of the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Publication 234, 1952, p. 56.

3. Cecil, R. L., and Loeb, R. F.: A Textbook of Medicine, ed. 8, Philadelphia, W. B. Saunders Company, 1951, p. 634.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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Main Office, Chicago...Members Throughout the United States

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- The Flavor Remains Stable down to the last tablet
- 15¢ Bottle of 24 tablets (2½ grs. each)

We will be pleased to send samples on request

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For CONSTIPATED BABIES

Borcherdt

MALT SOUP *Extract**

A gentle laxative modifier of milk. One or two tablespoonfuls in the day's formula—or in water for breast fed babies—produce a marked change in the stool.

SAVES DOCTOR'S TIME, TOO!
Fewer phone calls from anxious mothers. Malt Soup Extract is merely added to the formula. Prompt results. Easy for mother to prepare and administer. Does not upset the baby.

*Specially processed non-diastatic malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

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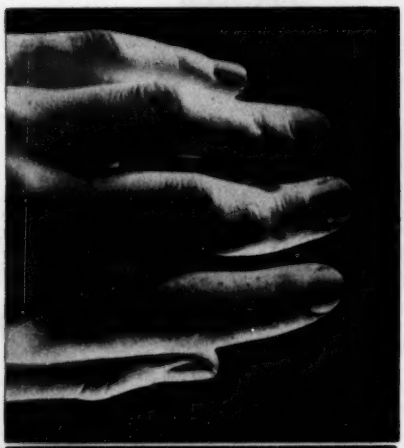

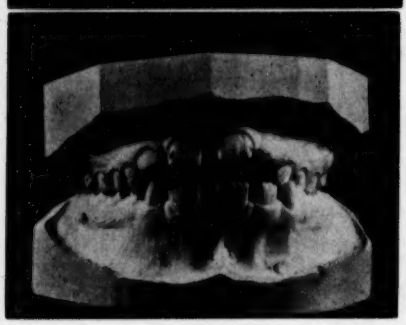

Untoward Results

OF PERSISTENT FINGER-SUCKING

MODEL

is 7½ years old. Unretouched photographs and description from a leading children's dental clinic.

Hand—sucked two middle fingers left hand since age 4. Note deformity caused.

Mouth—case shows deformed shape of mouth and displacement of teeth due to pressure of fingers.

WHEN TREATMENT IS INDICATED . . .
--prescribe
THUM TRADE MARK

Contains capsicum 2.34% in a base of acetone nail polish and isopropyl alcohol

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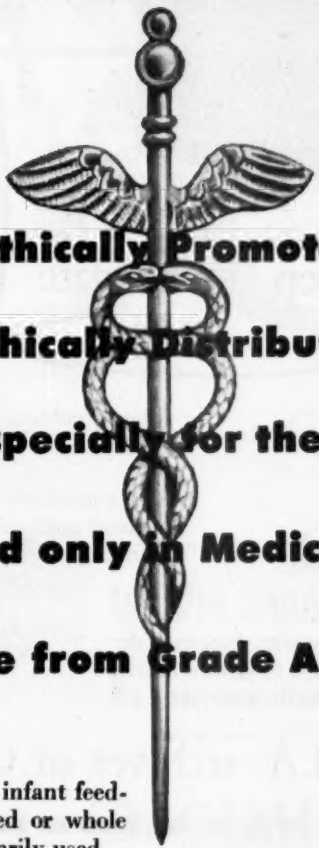

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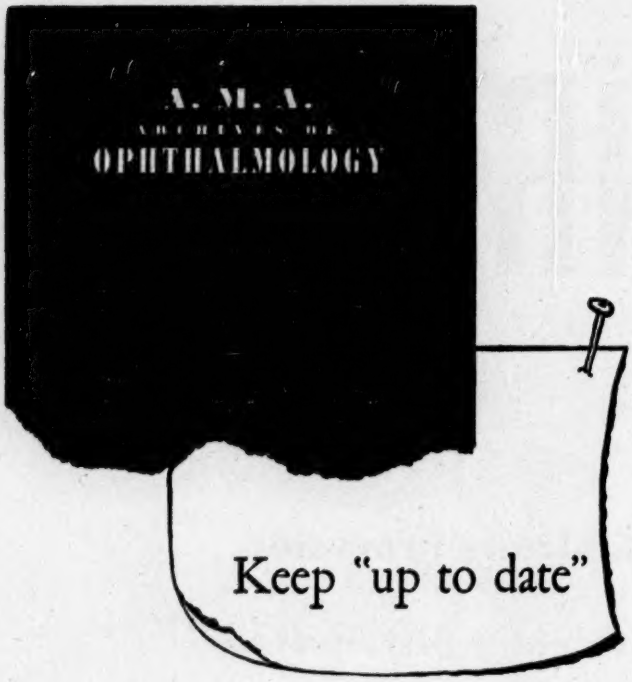

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pink milk

physiologically specific

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"... the recipe of the most satisfactory food for a baby."[2]

2. SIMILAC ®

so similar to the milk of healthy, well-nourished mothers that there is no closer equivalent.

Supplied: Similac Powder in tins of 1 lb., with measuring cup; Similac Liquid in tins of 13 fl. oz.

1. Bolliger, A., and Pascoe, J. V.: Australian Journal of Science *15*:215 (June) 1953.
2. Gunther, M.: Brit. J. Nutrition *6* (No. 2): 215, 1952.

M & R LABORATORIES, *Columbus 16, Ohio*

382.21

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Probana supplies high protein—part from a specially processed protein milk and part as a "predigested" casein hydrolysate. Fat, from the protein milk, is relatively low. Carbohydrate is supplied in the form of simple sugars, including those of banana powder.

The value of Probana has been established by years of intensive clinical investigation in hospitals and in private practice.

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Since Probana is specifically a therapeutic formula product, it is not stocked routinely in drug stores but is available through your druggist on request.

PROBANA

The therapeutic infant formula

1. Andersen, D. H.: Pediatrics 3: 406-417, 1949.
2. Detailed literature on Probana, including bibliography, is available on request.

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it ventilates . . .

because it affects diaphragm and intercostals . . . both! . . .

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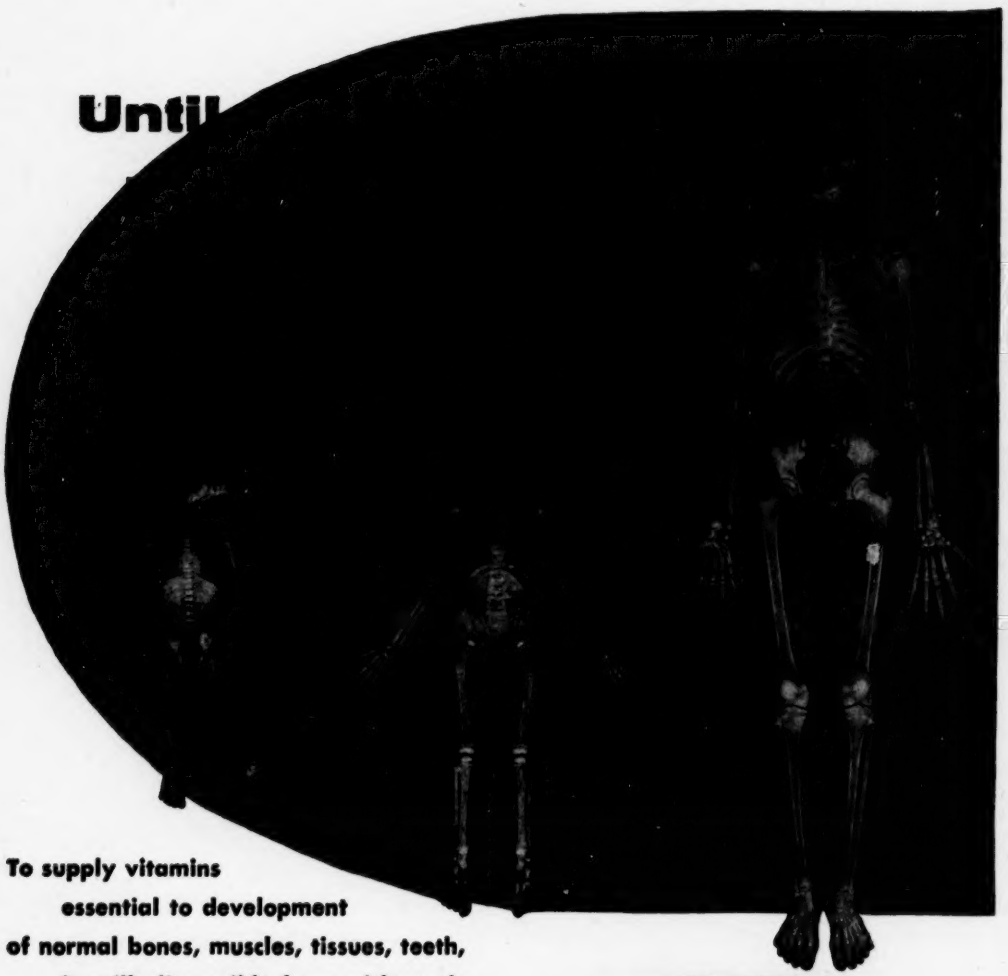

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